IDPA International Diatomite Producers Association

March 12, 1998

Dr. C.W. Jameson
National Toxicology Program
Report on Carcinogens (MD EC-14)
P.O. Box 12233
Research Triangle Park, NC 27709

RE: NTP Review of Crystalline Silica

Dear Dr. Jameson:

This letter is written to you on behalf of the International Diatomite Producers Association (IDPA), which is a trade association of producers of diatomaceous earth products that was formed in 1987 to study the health effects of these products. We urge NTP to consider all of the evidence in its review of crystalline silica. In doing so, it is our belief that you will come to the conclusion that "sufficient" evidence of human carcinogenicity in accordance with NTP criteria does not exist. Although IARC recently reclassified crystalline silica to Group 1, "carcinogenic to humans,"[1] we believe that the decision of IARC's Working Group on crystalline silica was flawed and not based upon an adequate scientific foundation. The state of the science reflected that a more limited designation for carcinogenicity is appropriate. In fact, a substantial number of the scientists in the IARC Working Group voted against the reclassification.

The study of diatomaceous earth workers[2] has been cited as providing strong evidence for a relationship between exposure to crystalline silica and lung cancer. This was based on an overall excess risk of lung cancer (SMR=1.43, 95% CI 1.09 - 1.84), a monotonic dose-response, and an elevated RR in the highest cumulative exposure cell of 2.74 (95% CI 1.38 - 5.46), as reported in the 1993 Checkoway et al. study of these workers. Subsequent studies, analyses, and reviews by the original investigators and others have shown that the earlier findings were overstated and misleading. The most recent analyses[3,4] indicate a significantly reduced overall excess risk (SMR=1.22, 95% CI 0.95-1.55), elimination of the monotonic dose-response, and a substantial reduction in highest cumulative exposure cell when asbestos exposure is accounted for.

In a 1997 review of a more recent seven-year follow-up study[5], Dr. Harland Austin noted that "[i]n epidemiologic terms, this excess (lung cancer risk) is small ...and a causal interpretation of the lung cancer findings is clouded by the potential that some, or all, of the excess may be due to chance or residual confounding by asbestos or smoking."[6]

In order for us to provide you with a more complete understanding of our assessment, we would like to share with you additional information about the diatomaceous earth worker studies that was not available to the IARC Working Group. The additional information raises serious questions about the strength of any conclusions that may have been drawn from these studies.

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Diatomaceous Earth Studies

History -

In 1987, with cooperation from the IDPA, Dr. Harvey Checkoway and his colleagues from the University of Washington School of Public Health undertook a cohort mortality study of workers employed in the diatomaceous earth industry. The first report on the study, *A Cohort Mortality Study of Workers in the Diatomaceous Earth Industry,*[7] was submitted to the IDPA by the investigators in October, 1992. The report, a copy of which is included herein, contains substantially more information about the study and its outcomes than provided in a condensed version published in 1993 by the British Journal of Industrial Medicine entitled, *Mortality among workers in the diatomaceous earth industry.*[2]

Following completion of the above study, additional information became available to the investigators which raised the question of more pervasive asbestos exposure to the cohort than originally reported. In 1994, Dr. Graham Gibbs and Dennis Christensen documented and quantified the findings in *The Asbestos Exposure of Workers in the Manville Diatomaceous Earth Plant, Lompoc, California.*[8] Their report was provided to Dr. Checkoway and was used as the basis of a re-analysis of the mortality study. A final report, co-authored by Drs. Checkoway and Gibbs, *Re-analysis of lung cancer among Diatomaceous Earth Industry Workers with Consideration of Potential Asbestos Exposure,*[9] was provided to the IDPA in February, 1996. As before, due to publication limitations, the report, a copy of which is contained herein, contains substantially more information than the version published later in 1996 in Occupational and Environmental Medicine, entitled *Re-analysis of mortality from lung cancer among diatomaceous earth industry workers, with consideration of potential confounding by asbestos exposure.*[10]

Most recently, an extended (seven-year) follow-up study on the cohort, funded by a NIOSH grant, was completed by Dr. Checkoway and his colleagues. The study report, *Dose-Response Associations of Silica with Non-malignant Respiratory Disease and Lung Cancer Mortality in the Diatomaceous Earth Industry,*[5] was published in the American Journal of Epidemiology (1997) followed by a report to NIOSH, *Silica, Silicosis, and Lung Cancer in Diatomite Workers.*[11] The results of this work were not published prior to IARC's October, 1996 Working Group discussions and thus were not cited in Monograph 68, *Silica, Some Silicates, Coal Dust and Para-Aramid Fibrils.*[1] A radiographic study on this cohort is expected to be published by the end of this year. The two most recent studies (follow-up and radiographic) are part of a joint effort by Dr. Checkoway and his colleagues at the University of Washington, and Dr. Hans Weill and his colleagues at Tulane Medical Center.

As noted, much of the information contained in these reports was not available to the IARC Working Group during their deliberations on crystalline silica. When incorporated with a working knowledge of the diatomaceous earth processing industry and its history, this body of information suggests that the conclusions reached by the investigators, and the ultimate interpretation by IARC's Working Group, were based upon significant study limitations that may have biased the interpretation.

Asbestos Exposure -

There were clearly two time periods when asbestos exposure to workers in the cohort was significant; in the pre-1930 period and again from 1951-1977.[8] Gibbs and Christensen reported that over 50% of the study population was either "definitely" or "probably" exposed to asbestos and that over 22% of the population were "definitely" or "probably" exposed for more than one year. The 1951-1977 workers comprised the majority of the known asbestos exposed workers,

however, one of the most critical concerns relates to the inclusion[2,5,7,11] in the cohort of 67 workers hired prior to 1930. The validity and strength of the study is based largely on this group of 67 workers. Their impact on the SMRs, the relative risks, the dose-response relationships, and conclusions is substantial, but their inclusion is not appropriate based upon all of the information available. Gibbs and Christensen[8] concluded that "asbestos was commonly used in the (Manville) plant in the 1920s" and that "the full extent of exposures is unknown. However, it is likely that exposures were several orders of magnitude greater than measured in the 1970s." Because the available data was not sufficient to develop job-specific exposure estimates, these workers were properly excluded from the re-analysis reports relating to asbestos exposure co-authored by Checkoway and Gibbs.[9,10]

These workers reappear in the follow-up study. The pre-1930 hires should not have been included in the mortality studies, and their inclusion artificially skews the "positive" findings.

As noted in the 1997 follow-up study reports,[5,11] some additional historical industrial hygiene information was uncovered by the investigators during the follow-up study period. However, it pertained primarily to dust levels after 1947 and not to asbestos exposure. In order to complete the asbestos exposure characterization for all periods of employment, the authors chose to extrapolate back to earlier periods the industrial hygiene data from the year 1930. In fact, according to Gibbs,[12] "... production workers were not assigned an asbestos exposure index in 1930," because there was no evidence of asbestos exposures in 1930. There was, however, extremely good evidence that asbestos exposures occurred in the plant during the 1920s. Thus, the assignment of a 1930 exposure level for asbestos, which was zero, to workers during the 1920's when asbestos exposure was known to have occurred, was improper. In his review of the follow-up study, Dr. Patrick Hessel[13] notes that "[s]ome questionable decisions were made, including: ...inclusion of workers employed prior to 1930 and the assignment of 1930 asbestos exposures for the pre-1930 period...." We do not believe that such extrapolations are valid, and the inclusion of these 67 workers represents a significant methodological flaw in the follow-up report.

In the period 1951-1977, a micropulverizer (grinder) was used to process the chrysotile fibers in the plant operation. Gibbs and Christensen[8] suggest that this processing led to fiber characteristics similar to those encountered in the asbestos textile industry.[14,15] This appears to be borne out by the elevated SMRs for some of the asbestos exposed workers. The same conclusion was reached by Dr. John Gamble[16] who conducted additional analyses of the report data and who also concluded that "[b]ecause of confounding from asbestos, the risk of lung cancer should be evaluated only in workers thought to have no asbestos exposures."

Elimination of these workers from the study cohort was, in fact, evaluated in earlier re-analysis reports[9,10] conducted prior to the recent follow-up study. The overall lung cancer SMR for the group with no asbestos exposure was 1.13 (95% CI, 0.73-1.69); for the group with any asbestos exposure it was 1.78 (95% CI, 1.18-2.57). The authors (Checkoway and Gibbs) noted that a risk gradient continued to be observed with crystalline silica among workers who had no apparent asbestos exposure. However, the trend was weaker than that reported previously[2,7] and was no longer statistically significant (nor were any other trend analyses). Thus, random chance could no longer be excluded as the cause of the numerical results.

In the follow-up study[5,11] (in the subset non-asbestos exposed, but including the pre-1930 workers), no increased risk is observed until the highest exposure category is reached (RR 2.03, CI 0.93-4.45), indicating the lack of any monotonic dose-response relationship. Other exposure categories starting with the lowest are 1.00, 0.73, 0.73, and 1.00 respectively. Further, the level of risk reached in the highest exposure cell in this analysis is questionable because, contrary to the asbestos exposure findings of Gibbs and Christensen[8], and as noted previously, the investigators assumed a ' zero' asbestos exposure for the majority of the pre-1930 hires. There was no valid reason for ignoring the work of Gibbs and Christensen, and the authors of the follow-up offered no explanation.

As a result of the above, additional, but separate, analyses of the diatomite worker follow-up study data by both Dr. Harvey Checkoway (University of Washington) and Dr. Janet Hughes (Tulane University) were conducted, excluding workers hired prior to 1930.[3,4] When these 67 workers were eliminated the dose-response remained non-monotonic and the level of risk reached in the highest exposure cell was substantially reduced and non-statistically significant (SMRs in ascending exposure categories were 1.37, 0.88, 0.82, 1.28, 2.21 respectively[4]).* Furthermore, the results of the separate analyses by both researchers show an additional reduction in overall lung cancer risk to the remaining study group from the SMR=1.29 reported in the follow-up study to an SMR=1.22. This represents a 25% reduction in excess risk. At the 95% confidence interval, the remaining excess was below the bounds of statistical significance, (95% CI, 0.95 - 1.55). Since the first cohort mortality study of diatomite workers was completed (early 90's), a reduction in excess risk of almost 50% has occurred (SMR=1.43 to 1.22). In addition, the dose-response relationship between cumulative crystalline silica exposure with the risk of lung cancer first reported in 1992 has virtually disappeared. While an excess risk continues to be observed in the highest cumulative exposure category, when all asbestos exposed workers are excluded, the result is no longer statistically significant.

* note: The follow-up study analysis was conducted using a RR calculation; the re-analysis (excluding asbestos exposed and excluding pre-1930 hires) was conducted using an SMR calculation.

Two factors appear to have caused this reduction: first, during the additional years of follow-up the excess risk essentially disappeared and, second, the development of asbestos exposure information from earlier decades showed that the silica risk was lower than previously thought. As a result, the causal relationship interpretation between crystalline silica and the risk of lung cancer drawn by the investigators is brought into question. It appears that more significance should have been placed on the impact of these asbestos exposed workers on the outcomes of the diatomite worker studies.

Misclassification biases -

One of the most fundamental issues in any epidemiological study is the presence and nature of a dose-response. The dose-response is in turn related to the validity and sufficiency of the exposure data, subsequent worker exposure assessments, and the choice of exposure category boundaries. In the original study,[2,7] due to a lack of dust exposure data prior to the 1950s, crystalline silica exposure assessments were made using a weighting scheme that attempted to take into account duration of exposure, intensity differences between job classifications and time periods, the use of respiratory protection devices, and the estimated percentages of crystalline silica in the various diatomaceous earth products. These estimates resulted in a series of multipliers or ordinals which placed most of the workers from the earliest periods into the highest exposure categories. In the seven-year follow-up study, the investigators developed semi-quantitative exposure estimates based upon air sampling records for the period 1948 - 1988 and extrapolated these data to earlier periods using an arbitrarily determined scale factor as was done in the original study. A comparison of the subjective exposure assessments used in the original study to the semi-quantitative estimates used in the seven-year follow-up study showed a large degree of undesirable overlap across all categories, suggesting a potential for misclassification.[17] Thus, serious questions have arisen regarding the assignment of crystalline silica exposures to all workers in the cohort, the extent of crystalline silica exposure to the earliest workers, and the validity of the scale factor used to assign exposures prior to 1944 in the follow-up study.

In discussing the difficulties of reconstructing exposure assessments, the principal investigator of the reconstruction noted that "[R]etrospective quantitative exposure assessment is by its nature replete with potential errors. While the availability of extensive industrial hygiene measurements greatly improves the potential for accurately estimating exposure levels, there are numerous sources of error which may still hamper the effort. The errors include sparse data for certain individuals, jobs or time periods, inappropriate, inaccurate or changing sampling and analytic methods, use of area samples to represent personal exposures and biased sampling strategies such as task-specific sampling or 'worst case' sampling. All of these sources of potential error are present to a substantial degree in the history of the cohort addressed here, and inherently limit the accuracy of the final results."[17]

Confounding from cigarette smoking -

In the 1993 study report, one of the tests suggested for consideration of confounding by smoking was to review the patterns of mortality for smoking related diseases, one of the sites being the larynx. It is interesting to note that the SMR for cancer of the larynx increased from 1.15 (95% CI 0.14-4.15) in the original study to 1.73 (95% CI 0.47-4.42) in the latest follow-up. Although the numbers are small, this suggests that the impact of smoking may have been understated. Furthermore as recently observed by Morgan and Reger[18] the elevated SMRs for emphysema in this cohort, both in the original study, 1.80 (95% CI 0.93-3.14) and the follow-up, 1.64 (95% CI 0.89-2.75) are also indicative of a significant impact of cigarette smoking.

When a 20-fold increase for lung cancer in smokers compared to non-smokers was assumed in the 1997 follow-up study, the rate ratio in the highest exposure category for crystalline silica decreased from 2.15 to 1.67. Given all of the other caveats associated with the elevated risk in this highest exposure grouping as discussed previously (asbestos exposure, exposure misclassification bias, etc.), one must conclude that the observed dose-response relationship, if it exists at all, is substantially weaker than reported.

Reference populations and local rates -

Most recently, the Office of Environmental Health Hazard Assessment (OEHHA), an agency of the California Environmental Protection Agency (Cal-EPA) released for public review a draft report entitled, *Illness Indicators in Lompoc California: An Evaluation of Available Health Data.*[19] The diatomaceous earth facilities whose workers were included in the Checkoway studies are located in the city of Lompoc, California. The report was prepared over concerns that pesticide use in the area may be causing health problems in the general population. The report states that "[i]ncidence of lung and bronchus cancers was elevated at the 99% statistical significance level; the increase was about 37% above the expected incidence," for the period 1988 - 1995. (The reference population was the three county area surrounding Lompoc including San Luis Obispo, Santa Barbara, and Ventura counties.) While this is morbidity data, it is more than suggestive of an increase in lung cancer mortality in the local geographical area. For the time period referenced (and for thirty years prior to that), no excess lung cancer risk was observed for the diatomite workers. This would suggest an environmental exposure in the local (Lompoc) area irrespective of occupation which is causing the elevated lung cancers, and may also be skewing the results from the worker studies. These findings by California's OEHHA suggest that the diatomite worker comparisons should be made to the immediate Lompoc vicinity and not to a national or wider multiple county area (as was done on the cohort mortality studies) in much the same manner as was conducted in the recent Staffordshire pottery workers studies.[20] Such comparisons would be expected to reduce the stated SMRs.

Summary

In summary, the uncertainties and questions surrounding the diatomaceous earth worker studies seriously challenge the interpretation of the findings drawn by the investigators regarding a causal relationship between exposure to crystalline silica and the risk of lung cancer, and further reduce scientific support for an overall conclusion that crystalline silica is a known human carcinogen. The evidence continues to be unconvincing for a direct relationship between exposure to crystalline silica and the risk of lung cancer in this cohort. In fact, given all of the limitations that could affect the validity and interpretation of the findings, Dr. Pat Hessel concluded that "[t]he diatomaceous earth workers at Lompoc are not a suitable population to explore the relationship between silica and lung cancer."[13]

In its review of crystalline silica, we urge the NTP to closely consider all of the above points in these studies, including in particular the:

- Substantial reductions in excess lung cancer risks indicated by the 7-year follow-up study and subsequent reanalyses (overall SMR to 1.22 with lower bound of 95% CI below the range of statistical significance);
- Lack of a monotonic dose-response when asbestos exposed workers are excluded (SMRs 1.37, 0.88, 0.82, 1.28, 2.21 in ascending cumulative exposure categories);
- Lack of statistical significance in the highest cumulative exposure cells; and
- Significant potential for exposure misclassification.

We would be more than happy to elaborate upon any of the points expressed in this letter or any questions that either you or members of the NTP Executive Committee Working Group for the Report on Carcinogens might have.

Sincerely,

Mel J. Mirliss
Executive Director

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RE-ANALYSIS OF LUNG CANCER AMONG DIATOMACEOUS EARTH INDUSTRY WORKERS WITH CONSIDERATION OF POTENTIAL ASBESTOS EXPOSURE

FINAL REPORT

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Introduction

Following publication of the findings from the University of Washington cohort mortality study of diatomaceous earth (DE) workers [Checkoway et al., 1993], there were suggestions that exposures to asbestos at the Manville plant may not have been fully recognized, and thus not taken into account in the analysis. Mortality data for a group of 104 workers with known prior asbestos exposures, primarily from mixing operations at the Manville DE plant, were analyzed separately from the main cohort data, although the full extent of possible asbestos exposure was not known at the time of the study. Accordingly, the International Diatomite Producers Association (IDPA) commissioned Gibbs and Christensen to perform an in-depth assessment of possible exposures to asbestos experienced by the cohort. Details are provided in a report to the IDPA [Gibbs and Christensen, 1994].

The goal of our re-analysis was to examine the exposure-response relation between crystalline silica and lung cancer mortality, while taking into account potential confounding from asbestos exposure. Also of interest were the possibilities that asbestos may have an independent association with lung cancer among DE workers and that asbestos may act synergistically with crystalline silica on lung cancer risk.

Methods

The re-analysis was performed among 2266 white male workers from the former Manville (now Celite) plant in Lompoc, California. Those were workers for whom it was possible to estimate potential asbestos exposures in DE operations. In addition to females and non-whites, excluded from this group were 66 workers hired before 1930, 327 workers who had been employed at the Grefco plant (299 only at Grefco; 28 also at Manville), and 8 workers with known asbestos exposure from employment prior to working at the Manville DE plant. Information on asbestos exposure of Grefco workers was not available; thus, they were excluded. Workers employed before 1930 were excluded because Gibbs and Christensen [1994] reported that there had been some use of asbestos at the Manville plant during that period, but felt that the information available to them was inadequate to make job-specific exposure estimates. Included in the re-analysis were 89 Manville workers who had worked in the Mortar Plant or Experimental/Specialty Products areas where asbestos exposure was known to have occurred (in the original report, data for these workers had been analyzed separately from the main study cohort).

Jobs were classified according to asbestos exposure potential by the method of Gibbs and Christensen [1994]. This scheme provided a classification of jobs as "not" exposed, "probably" exposed, or "definitely" exposed. Jobs classified as "possibly" exposed were considered to be only remotely likely to involve asbestos exposure for individuals who held them [Gibbs and Christensen, 1994]. Such jobs were therefore treated as "not" exposed in the analysis. The exposure reconstruction method of Gibbs and Christensen also enabled semi-quantitative estimates of asbestos levels (fibers/ml) for each job. The term 'asbestos' has been used throughout this report to refer to chrysotile used in the production and to other fiber types occasionally encountered in the mill or as part of maintenance and other activities. No attempt has been made in the this re-analysis to examine the specific role of individual fiber types.

In the original study, some jobs had been combined because of similarity of tasks and silica exposures. Other than identification of the two work areas involving asbestos exposure (Mortar Plant, Experimental Plant/Specialty Products), the potential for asbestos exposure was not considered when work history data were assembled in the original study. There were approximately 15% of the jobs analyzed in the original report [Checkoway et al., 1993] that, according to Gibbs and Christensen [1994], included component jobs with varying asbestos exposure levels. These jobs were assigned asbestos exposure ratings (none, probable, definite) and intensity levels (fibers/ml) by determining a weighted average asbestos level for the component jobs. To illustrate, consider the hypothetical case where a job category used in the original analysis encompassed 2 component jobs with similar silica exposures, but varying estimated asbestos levels. The estimated asbestos exposure intensity values for the component jobs are 1.0 and 0.5 fiber/ml, and the corresponding percentage contributions of work time to the overall job category are, respectively, 75% and 25%. Then, the estimated level would be (1.0 x 75%) + (0.5 x 25%) = 0.875 fibers/ml. For the exposure ratings (not exposed, probable, definite), we assigned to the combined job category, and hence to each component job, the rating contributed by the majority of work time contributed by the component jobs. If in the preceding example, the first job was classified as "definitely" exposed and the second as "probably" exposed to asbestos, then both jobs would be classified as "definite" because the first job contributed the majority (75%) of work time to the combined job category. The only combined jobs that were classified as "not exposed" to asbestos were those in which each component job was considered not to be exposed, as mentioned above.

We examined the influence of asbestos exposure on the lung cancer results in several ways. First, we computed the lung cancer Standardized Mortality Ratios (SMR) relative to mortality rates in U.S. white males during 1942-87 for: 1) the entire group of 2,266 workers included in the re-analysis; 2) the subset of workers who had either "probable" or "definite" asbestos exposure, of any duration, at any times during employment at Manville; and 3) workers who had neither "probable" nor "definite" exposure to asbestos at Manville.

Next, SMRs were computed for joint strata of workers defined by cumulative exposures to crystalline silica and asbestos. The crystalline silica index and the corresponding exposure strata were the same as reported in the original study [Checkoway et al., 1993]. As in the original study, cumulative exposures were lagged by 15 years to allow for a period of disease latency. Cumulative exposures to asbestos were computed using the quantitative exposure index derived by Gibbs and Christensen [1994]; a 15-year exposure lag was included here as well. Four increasing strata of cumulative asbestos exposure (fiber/ml x yr) were defined as: 0, >0-<2.7, 2.7-<6.8, and ≥6.8. Boundaries for the greater than 0 fiber/ml x yr strata were set to permit comparability with findings from a well-known study of U.S. asbestos textile workers [Dement et al., 1994]. Statistical test of trends for SMRs [Breslow and Day, 1987] were also performed for categories of cumulative exposures to crystalline and silica and asbestos.

We also conducted SMR analyses with respect to crystalline silica and duration of asbestos exposure. Additionally, lung cancer SMRs were estimated in reference to crystalline silica after sequentially eliminating workers: 1) with any "definite" asbestos exposure; 2) >1 year "definite" exposure; 3) >1 year "probable" exposure; and 4) any asbestos exposure. In these analyses, workers were eliminated based on potential exposures to asbestos <u>at any times</u> during employment at Manville, i.e., without imposing a lag interval. SMR trend tests were included in these analyses.

Finally, internal exposure-response analyses were performed for crystalline silica and asbestos by means of Poisson regression modeling [Breslow and Day, 1987]. Relative risk gradients were computed for each exposure, with and without statistical control for the other. In the controlled analyses, the exposure of interest was treated as a categorical variable whereas the other exposure, considered as a potential confounder, was left in a continuous form. As before, all exposures were lagged by 15 years. Thus, for example, in the trend analysis for the association with crystalline silica, relative risk estimates were derived for the four crystalline silica index categories (<50, 50-99, 100-199, and ≥200), and asbestos exposure (fiber/ml x years) was a treated as a continuous variable. Statistical control for age, calendar year, duration of follow-up, and ethnicity (Hispanic vs. non-Hispanic) was maintained throughout the internal trend analyses (see Checkoway et al., 1993 for a description of the Poisson regression modeling approach).

The potential for confounding, by cigarette smoking, of the observed association between crystalline silica and lung cancer was examined by two methods adopted in the original study [Checkoway et al., 1993]. We estimated the prevalence of cigarette smoking, by cumulative levels of crystalline silica, that would be required to render the observed exposure-risk relation null. These calculations were performed in reference to the relative risk gradient for crystalline silica, adjusted for asbestos exposure. The second approach was a computation of the joint distribution of crystalline silica exposure and prevalence of cigarette smoking (ever vs. never). Smoking data available from the Manville medical surveillance program were used for this purpose.

Results

The lung cancer SMR among the entire group of 2266 white male workers was 1.41 (52 observed). According to the exposure classification scheme of Gibbs and Christensen [1994], 1268 workers had either "probable" or "definite" asbestos exposure, and 998 had none. The lung cancer SMRs in these two strata were, resepctively, 1.78 (28 observed) and 1.13 (24 observed) (Table 1). No exposure or work history lagging was performed in calculating the any of the results in Table 1.

The cross-classification of person-years of observation by categories of crystalline silica and asbestos cumulative exposures are given in Table 2. The majority of person-time falls into the joint lowest stratum of crystalline silica and asbestos (<50/0, respectively). This occurred because all workers' exposures began at zero, and increased over time. The 15-year lag also contributes to the clustering of person-years in the top left cell of the table. It is noteworthy that, in the remainder of the table, person-time is widely distributed, which indicates a low correlation between cumulative exposures to the two agents (a high level of correlation would have been evidenced had most of the person-years been concentrated along the diagonal from top left to bottom right, i.e., from the 50-99/>0-<2.7 to ≥200/≥6.8 cells).

The cross-classified SMR results (Table 3) are numerically unstable because of small numbers of observed lung cancers. Nonetheless, these data permit approximate comparisons of the relative contributions of crystalline silica and asbestos to excess lung cancer mortality. Among workers not exposed to asbestos (top row of data) there is a reasonably consistent pattern of increasing mortality with cumulative exposure to crystalline silica. In contrast, the trend for asbestos exposure among workers with the lowest crystalline silica exposures (left column of data) is irregular. None of the SMR trends with respect to crystalline silica or asbestos exposure reached the conventional level of $p<0.05$ of statistical significance. The excess in the joint stratum of highest crystalline silica and asbestos exposure (SMR=8.31) is striking, despite being based on only 3 deaths.

Cross-classified SMRs with respect to crystalline silica and duration (rather than estimated cumulative exposure) to asbestos (Table 4) show a similar pattern to the data in Table 3, although the joint effect of the two exposures (SMR=2.93 in the highest joint stratum) is less prominent than that seen in Table 3. No trend shown in Table 4 was statistically significant.

SMR trends with respect to crystalline silica were computed after elimination of various subsets of asbestos-exposed workers (Table 5). Elimination of workers from these analyses were based on review of potential asbestos exposures throughout entire employment periods, without regard to lag (latency) interval. Thus, for example, the rightmost column of Table 5 excludes workers who had held jobs entailing either "definite" or "probable" asbestos exposures at any times during their employment at Manville. The lung cancer patterns fluctuate somewhat, but generally demonstrate a consistent pattern of elevated risk in the highest crystalline silica exposure categories. It is noteworthy that increased risks at the highest exposure levels remained evident when all asbestos-exposed workers were eliminated from the analysis (rightmost data column), and that this trend was closest to reaching statistical significance.

The internal exposure-response trend, based on Poisson regression modeling, is consistent with the SMR patterns (Table 6). Control for asbestos exposure made barely perceptible differences in the relative risk estimates, which re-confirms that asbestos was not an important confounder. Also consistent with the SMR findings is the large excess among workers with the highest cumulative asbestos exposures (adjusted RR=4.59 for workers with $\geq$6.8 fiber/ml x yrs), detected from internal risk comparisons (Table 7). In order to assess the relative effects of the two exposures, we computed relative risks associated with 1 year at 10 cumulative exposure units to crystalline silica (the cohort's mean level) and 1 fiber/ml x yr of asbestos (Table 8). The interpretation of these data is that each increment of exposure of either type would produce a 1 percent increase in lung cancer relative risk compared to the lowest exposure category. Mutual control for the other agent did not alter the slope estimates, which was expected in view of the previously demonstrated absence of confounding. The confidence intervals for these slopes were also remarkably similar. Although the relative risk slopes and associated confidence intervals are similar, they cannot be used to compare the relative potencies of crystalline silica and asbestos because the exposure units for these exposures are quite different.

The smoking prevalence distributions required to eliminate the exposure-response gradient for crystalline silica, adjusted for asbestos exposure, under varying estimates of smoking prevalence in the reference category (ranging from 0.3 to 0.7), are given in Table 9. These estimates were generated under the assumption that there is an independent relative risk of 10 associated with smoking. A very strong relation between smoking and exposure would have been necessary for smoking to have been solely responsible for the observed risk gradient. Moreover, it would be virtually impossible for the relative risks in the highest two exposure categories (1.80, 1.79) to be explained by smoking when the baseline prevalence of smoking is set at 0.7, a value that may even be an underestimate for this cohort. Smoking data from the Manville medical surveillance program could only be examined in relation to exposure for workers born during the years 1900-1939; there was no smoking information for workers in various crystalline silica exposure categories for workers born before and after those dates. Based on the available data, there was no evidence of confounding, as smoking prevalence was uniformly distributed across exposure levels (Table 10).

Discussion

The possibility that the observed association between crystalline silica and lung cancer was confounded by asbestos exposures has been evaluated in the Manville segment of the cohort for which the most reliable asbestos exposure information was available. The asbestos exposure assessment was conducted independently of the previous assessment of crystalline silica exposures, and without knowledge of cohort members' mortality outcomes. Thus, a biased classification scheme is unlikely to have been produced.

Our re-analysis demonstrates that asbestos exposure was not an important confounder. In fact, the amount of confounding from asbestos exposure was at most minor. The lack of correlation between cumulative exposures to crystalline silica and asbestos support this conclusion. Also, a reasonably strong risk gradient was observed with crystalline silica among workers who had no apparent asbestos exposure. This gradient is not as strong as the trend reported previously [Checkoway et al., 1993]. One of the more probable explanations for the apparently diminished lung cancer mortality pattern with crystalline silica is that workers hired before 1930, for whom the original lung cancer excess was largest (SMR=2.63), were not included in this re-analysis. It is also highly unlikely that cigarette smoking was a confounder.

Although asbestos exposure does not appear to have confounded the observed relation of lung cancer with crystalline silica, our findings indicate that asbestos exposure may have contributed to lung cancer risk among some members of the cohort. A firm conclusion cannot be reached regarding the extent of the association of lung cancer mortality with asbestos exposure in the Manville plant because the elevated risk was concentrated among the workers with the heaviest asbestos exposures ($\geq$6.8 fibers/ml x yrs), and was based on only 4 deaths. The data also suggest the possibility of an interaction (synergy) between exposures to crystalline silica and asbestos. Evidence for this is almost entirely due to a large relative excess among workers who experienced the highest cumulative exposures to both dusts. Synergy between lung carcinogens (e.g., radon and tobacco smoke) has been reported in other studies. A fuller evaluation of possible independent and interactive effects of crystalline silica and asbestos in this cohort may be possible when the number of lung cancer deaths increases after the extended mortality follow-up through 1993 is completed.

Radiographic information that is being obtained in the ongoing cohort study update, in particular the prevalence of pleural abnormalities by period of employment, should provide further insight into the possible magnitude of asbestos exposure in these DE facilities.

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Table 1

Lung Cancer Mortality Among 2,266 Manville White Males According to Asbestos Exposure Status*

Group	No. of workers	Observed	SMR†	(95% CI)‡
No asbestos exposure	998	24	1.13	(0.73-1.69)
Any asbestos exposure	1268	28	1.78	(1.18-2.57)
Total	2266	52	1.41	(1.05-1.85)

*Asbestos exposure refers to ever employed in a job, at any time (i.e., without exposure lagging), classified as "definite" or "possible" by Gibbs and Christensen (1994).

†Based on rates for U.S. white males, 1942-87

‡95 percent confidence interval

Table 2

Person-Year Distribution by Cumulative Exposure to Crystalline Silica and Asbestos, Each Lagged 15 Years: 2,266 Manville White Males

Asbestos index (fiber-years)		Crystalline Silica Index† <50 [7.15]*	50-99 [70.0]	100-199 [142]	≥200 [364]
0	[0]*	33,117 (62.1)**	2618 (4.9)	2152 (4.0)	1771 (3.3)
>0-<2.7	[0.95]	6397 (12.0)	1952 (3.7)	1237 (2.3)	744 (1.4)
2.7-<6.8	[4.14]	917 (1.7)	786 (1.5)	474 (0.9)	264 (0.5)
≥6.8	[18.7]	440 (0.8)	142 (0.3)	104 (0.2)	224 (0.4)

†From Checkoway, et al. (1993).

‡Derived from Gibbs and Christensen (1994).

*Mean crystalline silica or asbestos exposure index

**Percent of total (53,339)

Table 3

Lung Cancer Standardized Mortality Ratios (SMR) by Cumulative Exposure to Crystalline Silica and Asbestos, Each Lagged 15 Years: 2,266 Manville White Males

Asbestos index f/ml x yrs	Crystalline Silica Index ≤50 (Obs)	SMR†	50-99 (Obs)	SMR†	100-199 (Obs)	SMR†	≥200 (Obs)	SMR†	Total (Obs)	SMR†	*p*-for trend
0	(15)	1.13 [0.63-1.86]‡	(3)	0.87 [0.18-2.53]	(7)	2.14 [0.86-4.41]	(6)	2.00 [0.73-4.35]	(31)	1.34 [0.91-1.91]	0.12
>0-<2.7	(4)	0.83 [0.23-2.13]	(5)	2.35 [0.76-5.48]	(2)	1.11 [0.13-4.03]	(1)	0.59 [0.01-3.30]	(12)	1.15 [0.59-2.01]	0.92
2.7-<6.8	(3)	4.63 [0.95-13.5]	(1)	1.20 [0.03-6.69]	(1)	1.66 [0.04-9.26]	(0)	0 [0-8.44]	(5)	1.99 [0.65-4.64]	0.12
≥6.8	(0)	0 [0-16.1]	(0)	0 [0-23.8]	(1)	6.03 [0.15-33.6]	(3)	8.31 [1.71-24.3]	(4)	4.40 [1.20-11.3]	0.09
Total	(22)	1.16 [0.73-1.75]	(9)	1.37 [0.62-2.59]	(11)	1.89 [0.94-3.37]	(10)	1.82 [0.87-3.35]	52	(1.41) [1.05-1.85]	0.14
p-for trend		0.46		0.61		0.89		0.23		0.11	

†Based on rates for U.S. white males, 1942-87

‡95 percent confidence interval for SMR

Table 4

Lung Cancer Standardized Mortality Ratios (SMR) by Cumulative Exposure to Crystalline Silica and Duration of Exposure to Any Level of Asbestos*

Duration of asbestos exposure (yrs)	Crystalline Silica Index ≤50 (Obs)	≤50 SMR†	50-99 (Obs)	50-99 SMR†	100-199 (Obs)	100-199 SMR†	≥200 (Obs)	≥200 SMR†	Total (Obs)	Total SMR†	p-for trend
0	(15)	1.13 [0.63-1.86]‡	(3)	0.87 [0.18-2.53]	(7)	2.14 [0.86-4.41]	(6)	2.00 [0.73-4.35]	(31)	1.34 [0.91-1.91]	0.12
>0-<5	(7)	1.25 [0.50-2.58]	(5)	1.89 [0.62-4.42]	(2)	1.03 [0.12-3.71]	(0)	0 [0-3.28]	(14)	1.24 [0.68-2.08]	0.39
≥5	(0)	0 [0-36.9]	(1)	2.10 [0.05-11.7]	(2)	3.26 [0.39-11.8]	(4)	2.93 [0.80-7.51]	(7)	2.74 [1.10-5.65]	0.63
Total	(22)	1.16 [0.73-1.75]	(9)	1.37 [0.62-2.59]	(11)	1.89 [0.94-3.37]	(10)	1.82 [0.87-3.35]	52	(1.41) [1.05-1.85]	0.14
p-for trend	0.89		0.27		0.92		0.71		0.27		

*Each lagged 15 years

†Based on rates for U.S. white males, 1942-87

‡95 percent confidence interval for SMR

Table 5

Lung Cancer Standardized Mortality Ratios (SMR) by Cumulative Exposure to Crystalline Silica, Lagged 15 Years, with Varying Exclusions of Asbestos-Exposed Workers

	Exclusion									
Crystalline Silica Index	None		Any "definite" asbestos exposure		"Definite" asbestos exposure>1 yr		"Probable" asbestos exposure>1yr		Any asbestos exposure§	
	(Obs)	SMR†	(Obs)	SMR†	(Obs)	SMR†	(Obs)	SMR†	(Obs)	SMR†
<50	(22)	1.16	(14)	0.97	(21)	1.17	(14)	0.96	(9)	0.78
	[0.73-1.76]‡		[0.53-1.63]		[0.72-1.79]		[0.52-1.61]		[0.36-1.48]	
50-99	(9)	1.37	(7)	1.43	(9)	1.42	(6)	1.31	(3)	0.88
	[0.63-2.60]		[0.57-2.94]		[0.65-2.69]		[0.48-2.85]		[0.18-2.57]	
100-199	(11)	1.89	(10)	1.98	(11)	1.94	(8)	1.90	(7)	2.16
	[0.94-3.38]		[0.95-3.64]		[0.97-3.47]		[0.82-3.74]		[0.87-4.45]	
≥200	(10)	1.82	(8)	1.59	(8)	1.54	(5)	1.47	(5)	1.71
	[0.87-3.35]		[0.68-3.13]		[0.66-3.04]		[0.48-3.43]		[0.56-4.00]	
Total	(52)	1.41	(39)	1.33	(49)	1.40	(33)	1.23	(24)	1.13
	[1.05-1.85]		[0.94-1.81]		[1.04-1.85]		[0.85-1.73]		[0.73-1.69]	
p-for trend	0.14		0.12		0.24		0.18		0.05	

†Based on rates for U.S. white males, 1942-87

‡95% confidence for SMR

§Excludes workers classified as having had "definite" or "probable" asbestos exposure, of any duration, at any time during employment at Manville

Table 6

Lung Cancer Relative Risks Associated with Cumulative Exposures to Crystalline Silica, with and without Adjustment for Asbestos Exposure

Crystalline silica index	No. deaths	Without adjustment* RR†	(95% CI)	With adjustment* RR†	(95% CI)
<50	22	1.00	—	1.00	—
50-99	9	1.38	(0.61-3.09)	1.37	(0.61-3.08)
100-199	11	1.81	(0.83-3.94)	1.80	(0.82-3.92)
≥200	10	1.83	(0.79-4.25)	1.79	(0.77-4.18)

*Adjustment for cumulative f/cc x yr, lagged 15 years

†Relative risk adjusted for age, calendar year, duration of follow-up, ethnicity (Hispanic vs. non-Hispanic), by Poisson regression modeling

Table 7

Lung Cancer Relative Risks Associated with Cumulative Exposures to Asbestos, with and without Adjustment for Crystalline Silica Exposure

Asbestos index f/ml x yrs	No. deaths	Without adjustment RR†	Without adjustment (95% CI)	With adjustment* RR†	With adjustment* (95% CI)
0	31	1.00	—	1.00	—
>0-<2.7	12	0.99	(0.49-1.98)	0.92	(0.45-1.88)
2.7-<6.8	5	1.99	(0.73-5.42)	1.74	(0.62-4.91)
≥6.8	4	5.62	(1.86-17.0)	4.59	(1.40-15.0)

*Adjustment for cumulative exposure to crystalline silica, lagged 15 years

†Relative risk adjusted for age, calendar year, duration of follow-up, ethnicity (Hispanic vs. non-Hispanic), by Poisson regression modeling

Table 8

Exposure-Response Slopes for Crystalline Silica and Asbestos with Lung Cancer Mortality

Exposure	Slope†	(95% CI)‡
Crystalline silica	1.01	(0.99-1.03)
Crystalline silica - adjusted for asbestos	1.01	(0.99-1.03)
Asbestos	1.01	(0.99-1.03)
Asbestos - adjusted for crystalline silica	1.01	(0.98-1.03)

†Relative risk associated with 1 year at 10 crystalline silica units or with 1 f/ml x yr

‡95 percent confidence interval for slope

Table 9

Proportionate Distribution of Smokers Required to Eliminate Observed Exposure-Response Trend for Crystalline Silica and Lung Cancer, Assuming a 15-Year Latency

Crystalline silica index	Observed RR*	Proportion of smokers in reference group 0.30	0.50	0.70
<50	1.00	0.30	0.50	0.70
50-99	1.37	0.45	0.73	1.00
100-199	1.80	0.63	0.99	[1.35]†
≥200	1.79	0.62	0.98	[1.34]†

*Relative risk, adjusted for age, calendar year, duration of follow-up, ethnicity (Hispanic vs. non-Hispanic), cumulative asbestos exposure

†[ ] number larger than 1.00 impossible

Table 10

Smoking Status by Estimated Cumulative Exposure to Crystalline Silica Lagged 15 Years: 1575 White Males Born 1900-1939

Crystalline silica index	No. workers with smoking data	No. of smokers	Percent smokers: Crude	Percent smokers: Adjusted to birth year of cohort†	Percent smokers: Adjusted to birth year of workers with smoking data‡
<50	236	198	0.84	0.82	0.83
50-99	126	111	0.88	0.89	0.88
100-199	100	81	0.81	0.83	0.81
≥200	77	65	0.84	0.84	0.83

†Adjusted to birth year distribution of all 1575 white males born 1900-1939

‡Adjusted to birth year distribution of 539 white males born 1900-1939 with available smoking data

FINAL REPORT

A COHORT MORTALITY STUDY OF WORKERS IN THE DIATOMACEOUS EARTH INDUSTRY

Submitted to:

The International Diatomite Producers Association

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EXECUTIVE SUMMARY

In 1988, the International Diatomite Producers Association (IDPA) contracted with researchers from the University of Washington School of Public Health and Community Medicine to conduct an epidemiologic cohort mortality study of workers employed in the mining and processing of diatomaceous earth (DE).

Diatomaceous earth is a mineral derived from the skeletal remains of diatoms that are deposited in marine and lake floors. The raw (natural) material consists of amorphous silica and is mined in open pits or quarries. The material is crushed and dried, and can be further processed by calcining in a kiln either with or without a flux (sodium carbonate or sodium chloride). The percentage of crystalline silica in the material depends on the process. Typically, natural DE contains 0.1-4 percent crystalline silica, mainly quartz from the earth's crust. The percentages of crystalline silica in the respirable fractions of calcined and flux-calcined DE are, respectively, 10-20 and 20-25 percent. Cristobalite is the principal form of crystalline silica in the calcined materials. DE has a wide range of commercial uses as a filtration aid for water, foods, and beverages, as filler in construction materials, paints, and insulation, and as a carrier or anti-caking agent for insecticides and other agricultural chemicals.

This study was prompted by the International Agency for Research on Cancer [IARC]'s 1987 conclusion that crystalline silica is a probable human carcinogen. IARC reported inadequate information on amorphous silica to make a determination of potential carcinogenicity. Prior to 1987, most attention in the DE industry focused on silicosis. As early as 1932, silicosis was identified as a hazard in the DE industry. Studies conducted by the U.S. Public Health Service in the 1950s, and updated subsequently, found that the initially excessive prevalence of silicosis among DE workers has been reduced over time as a result of improved dust control measures. To our knowledge, the present study is the first formal epidemiologic investigation of cancer risks in the DE industry.

The study group, or cohort, included workers from three companies who were employed for at least 12 months cumulative service in the industry and who were employed for at least one day between 1 January 1942 and 31 December 1987. The largest two plants, which comprise the majority of the study cohort, are located near Lompoc, California. Workers from two smaller plants, one in Nevada and one in eastern Washington State, were also included in the study. Originally, we intended to include data from a fourth company, with two small plants in Nevada; however, the data necessary for cohort enumeration were too incomplete for cohort construction. Therefore, data for this company's workers were not included in this report.

The cohort was enumerated from company personnel and work history records. Vital status was determined for the years 1942-1987, inclusive, using information from a number of sources, including the Social Security Administration tapes of mortality in the U.S., a similar data source for the State of California, the National Death Index, state motor vehicles bureaus, and credit bureaus. Copies of death certificates for deceased workers were obtained from state offices of vital statistics. Vital status was ascertained for 91 percent of the study cohort, and copies of death certificates were obtained for 94 percent of identified deaths.

Exposures to DE dust were estimated by combining information from work history records, available industrial hygiene monitoring data, and ratings of exposure levels made in consultation with senior industry personnel. Quantitative measurements of individual workers' actual dust exposures could not be made because of incompleteness of the historical industrial hygiene monitoring data. Instead, we devised several indices of cumulative dust exposure that incorporated qualitative differences in exposure levels between jobs and over time, the relative amounts of natural, calcined, and flux-calcined DE produced and handled in various jobs over time, and estimates of the corresponding percentages of crystalline silica in the respirable fractions of the dust for the three product types. The exposure assessment was performed in consultation with industry safety and occupational hygiene representatives.

The majority of the cohort consisted of workers from the two Lompoc plants. Among the Lompoc workers, there were 2,674 white males (including Hispanics and non-Hispanics), 37 black males, 242 white females, and 8 black females. There were too few black females and no deaths among them to conduct a meaningful analysis. Review of the work history information revealed that 104 white males also had potential past exposures to asbestos. These workers were considered separately to avoid confounding the results related to DE exposure with the potential effects attributable to asbestos. The cohorts for the Nevada and Washington State plants consisted of 158 and 121 white males, respectively. The most detailed analyses were performed on the data for the 2,570 Lompoc white males without evidence of past asbestos exposure. These results are described below, and are followed by a summary of findings for the other groups of workers.

The analysis of the data for the 2,570 Lompoc white males was conducted in two phases. The first set of analyses was performed to identify mortality excesses and deficits among the workers compared to expected rates in the general population. White males in the U.S. population were the main reference group. These mortality rate comparisons involved calculations of Standardized Mortality Ratios (SMRs). An SMR is the ratio of the number of observed deaths from a specific disease among the study cohort divided by the expected number of deaths from that cause. The expected number is estimated by applying the rates in the reference (U.S.) population to the numbers of person-years of observation in the cohort. Thus, an SMR of 1.0 for a given disease means that there is neither an excess nor a deficit of mortality from that cause in the cohort. An SMR greater than 1.0 suggests an excess, whereas an SMR less than 1.0 indicates a mortality deficit.

Mortality from all causes combined during 1942-87 was slightly elevated among the 2,570 Lompoc white males compared to the U.S. population (SMR=1.12; 628 observed deaths). This overall excess was primarily explained by increased rates of non-malignant respiratory diseases (SMR=2.59; 56 deaths) and lung cancer (SMR=1.43; 59 deaths). The category of non-malignant respiratory diseases (NMRD) includes pneumoconiosis, emphysema, asthma, and bronchitis (pneumonia and infectious respiratory diseases were not included in this category). Unfortunately, death certificate information is not sufficiently reliable to permit an accurate determination of silicosis, which is the NMRD condition of most relevance to the DE industry. Mortality from cardiovascular diseases was below national rates, as is typically seen in industrial cohorts. The lung cancer excess increased slightly when local county rates for southern California were used for comparison. This suggests that the lung cancer excess in the cohort was not merely due to variations in geographic patterns of risk, data reporting, or diagnostic custom.

The second set of analyses for the 2,570 Lompoc white males was an in-depth assessment of the relationships between DE exposure and mortality risks from lung cancer and NMRD. The objective of these analyses was to explore for evidence of dose-response relationships. Observation of an apparent dose-response relationship can strengthen evidence supporting causal associations in epidemiologic research. In these analyses, mortality rates were compared between subgroups of the cohort classified by exposure duration and level. The measure of effect in such analyses is the relative risk (RR). The numerical values of RR (<1.0, 1.0, >1.0) are interpreted in the same manner as those of the SMR.

Mortality gradients were examined with respect to four exposure indices: (1) total duration of employment in the DE industry; (2) duration of employment in dust-exposed jobs; (3) duration of employment in dust-exposed jobs weighted by exposure intensity; and, (4) estimated cumulative exposure to crystalline silica. The weighted dust index (#3) included duration of employment in dust-exposed jobs, differences in exposure intensity between jobs and over calendar time periods, and estimates of the effectiveness of respiratory protective devices. Index #4, cumulative exposure to crystalline silica, included all of the elements of #3, as well as estimates of the relative amounts of the various DE materials produced and handled (natural, calcined, and flux-calcined) over time, and the corresponding percentages of crystalline silica in the respirable dust of the three types of DE.

The relative risks (RR) for both lung cancer and NMRD generally increased with increasing exposure level for the various exposure indices. We place greatest emphasis on the findings pertaining to cumulative crystalline silica exposure because this was the principal a priori concern of the study. The trend of RR values, allowing for a 15-year lag time (latency) between exposure and mortality, from the lowest (reference) to the highest crystalline silica exposure category was: 1.00, 1.19, 1.37, and 2.74. This implies that the risk for lung cancer among workers with the highest cumulative exposures to crystalline silica was roughly 2.7 times that of workers with the lowest exposures. The corresponding trend for NMRD, also allowing for a 15-year lag between exposure and mortality, was: 1.00, 1.13, 1.58, and 2.71.

The potentially confounding effect of cigarette smoking in an epidemiologic study is a threat to validity, especially in instances where lung cancer and other respiratory diseases are of primary interest. The potential for confounding by smoking was examined in a variety of ways. First, we evaluated mortality data for smoking-related diseases other than lung cancer and NMRD. The other smoking-related diseases include cancers of the oral cavity, esophagus, larynx, pancreas, urinary bladder, and kidney. No mortality excesses from these diseases were detected.

A second approach for examining the possibility of confounding involved analyses of the available data on smoking that were obtained from company medical records. Smoking data were available for 1,113 of the 2,570 cohort members. There appeared to be a slight correlation between smoking and crystalline silica exposure among the 1,113 workers; however, no correlation was seen for the subset of 544 workers with available smoking data who were born between 1890 and 1930. A separate analysis of the lung cancer trend according to crystalline silica exposure was performed among all 1,765 cohort members who were born between 1890 and 1939. This was done to assess the exposure-response gradient among workers for whom smoking patterns appeared to have been unrelated to exposure level. This analysis yielded nearly identical results to those found for all 2,570 members of the Lompoc cohort. Finally, we conducted a separate analysis of lung cancer in relation to crystalline silica exposure among the group of 768 workers identified from the available medical history data as cigarette smokers; again, an apparent dose-response trend was noted.

On balance, the analyses that were conducted to assess confounding revealed that it was unlikely that the risk gradients observed between cumulative crystalline silica exposure and lung cancer mortality were solely the result of confounding by smoking. However, more complete and detailed data on smoking would be needed to reach firm conclusions about the complete extent of potential confounding by smoking, and the possible synergy between DE dust exposure and smoking.

Hispanic ethnicity is another potential confounder because Hispanic white males historically have had lower lung cancer risks than non-Hispanic white males. Potential confounding by Hispanic ethnicity was controlled in the comparisons between worker subgroups by means of statistical adjustments.

Asbestos, which is another known risk factor for lung cancer and NMRD, was used at various times in one of the plants. We were able to identify 104 workers who had probable asbestos exposures from employment in the DE industry and from previous occupations. Data for these workers were analyzed separately from the remainder of the cohort, thus eliminating confounding from asbestos exposure.

Because of the small size of the other groups of DE workers, the data analyses were limited to SMR comparisons against prevailing rates in the U.S. population. With the exception of the cohort from the Washington State plant, excesses of lung cancer and NMRD were seen consistently in all other groups. These findings were based on small numbers of workers and deaths, and thus inferences derived from any of the specific findings are necessarily limited.

An assessment of the strengths and limitations of the study is necessary for interpreting the findings. The study's strengths include the long period of follow-up, over 40 years, the analysis of complete occupational history for the Lompoc cohort which permitted estimation of dose-response relationships, and the use of internal reference groups which minimized biases that often arise from comparisons against external reference populations. The principal limitations of the study were incomplete vital status and cause of death ascertainment, the lack of sufficient industrial hygiene data to permit quantitative estimation of dose-response relationships for crystalline silica, and the limited information available on cigarette smoking. Also, the reliance on death certificate data for the study of NMRD, and more specifically for silicosis, was a limitation because death certificate information typically is inadequate for identifying and correctly classifying specific forms of NMRD. None of the study's limitations is likely to have produced severe bias in the study. Of greatest concern is the possibility of confounding by smoking, which we have shown using several approaches, is not likely to have fully accounted for the excesses of lung cancer and NMRD.

The results for lung cancer and NMRD indicate that the excesses were most likely attributable to relatively intense exposures encountered during the 1930s and 1940s, before dust control measures were implemented on a wide-scale basis in the industry. At present, it cannot be said with certainty that lung cancer and NMRD risks have been reduced to baseline levels experienced by the population at large. However, it is noteworthy that there has been no excess risk of lung cancer among Lompoc cohort workers hired since 1960, and there have been no deaths attributed to silicosis among cohort members hired since 1950. These trends are strongly suggestive of reduced hazards, probably related to improved environmental dust control and the increased use of respiratory protective devices by the workforce.

We place most emphasis on the findings for the Lompoc white male cohort because it represents the largest group of DE workers in the study, and because exposure assessment was most complete for these workers. Based on the findings from our epidemiologic analysis, we offer the following conclusions:

1. There have been excesses of lung cancer and non-malignant respiratory disease (NMRD) mortality among DE workers compared to the national and regional populations.

2. The estimated dose-response trends for lung cancer and NMRD with DE dust exposure, especially the crystalline silica content of the dust, are consistent and reasonably strong, and thus indicate a causal role of occupational exposures.

3. It is unlikely that confounding by cigarette smoking can fully explain the overall lung cancer and NMRD excesses or the apparent dose-response trends. Confounding by either asbestos exposure or Hispanic ethnicity is also an unlikely explanation for the results.

4. Relatively intense exposures that occurred before the 1950s were probably the most important occupational contributors to the excess lung cancer and NMRD risks.

5. The time trends of lung cancer and NMRD mortality indicate risk reductions, possibly due to improvements in dust control.

6. Further mortality follow-up of the cohort, accompanied by the accumulation of more detailed exposure and smoking data, will be needed to determine the extent to which exposure abatement efforts have been successful in diminishing mortality risks.

7. The long-term trend of silicosis occurrence and its relationship with dust exposure control measures will require cohort analyses of workers' x-ray and exposure data. This would also permit an examination of the relationship between silicosis and lung cancer risk.

Additional years of observation of the mortality of DE workers will be needed before the effects of exposure reduction in the industry can be fully discerned. In the interim, it would be prudent for the industry to continue ongoing exposure reduction and medical surveillance programs. In addition, we recommend that further efforts be made to conduct industrial hygiene surveys that will permit thorough, quantitative estimates of workers' personal exposures. Finally, we recommend systematizing the collection and storage of the personnel, job history, and exposure monitoring data necessary for epidemiologic follow-up studies of DE industry workers.

CHAPTER I

BACKGROUND

In 1988, the International Diatomite Producers Association (IDPA) contracted with researchers from the University of Washington School of Public Health and Community Medicine to conduct an epidemiologic cohort mortality study of workers employed in the mining and processing of diatomaceous earth (DE). The study was prompted by concerns that crystalline silica may be a human carcinogen. DE is a mixture of amorphous and crystalline silica, with the crystalline component consisting mainly of cristobalite. In a 1987 monograph, the International Agency for Research on Cancer [IARC, 1987a] summarized evidence from experimental and epidemiologic studies of silica, and concluded that "there is limited evidence for the carcinogenicity of crystalline silica to humans." Later that year, IARC [1987b] classified silica as a probable human carcinogen. IARC also concluded that there was "inadequate evidence for the carcinogenicity of amorphous silica to experimental animals or humans."

Prior to 1987, most attention on health risks in the DE industry was focused on silicosis. In 1932, Legge and Rosencrantz described the findings of a survey which revealed a nearly 70 percent prevalence of radiographically-determined silicosis among Mexican DE laborers in California. There have been subsequent case series reports of silicosis among workers exposed to DE in the U.S. [Caldwell, 1958], Italy [Vigliani and Mottura, 1948], and Sweden [Beskow, 1978]. Based on their the review of chest x-rays and occupational histories of DE workers, Smart and Anderson [1952] suggested that calcined and flux-calcined DE dust, which contain high free silica contents, can induce a rapid progressive lung fibrosis, and that the raw DE, which contains primarily amorphous silica, can produce less aggressive, yet radiographically detectable, fibrotic changes.

Concern about silicosis in the DE industry in California heightened in the early 1950s following the appearance of articles in the lay press concerning silicosis in the industry and a strike in 1952 in which adverse health effects was a major issue [Abrams, 1954; 1990]. In 1957, the U.S. Public Health Service conducted a radiographic survey of 869 workers at five DE plants located in California, Nevada, and Oregon [Cooper and Cralley, 1958]. The survey revealed a 9 percent prevalence of "probable" silicosis and 9 percent "doubtful" silicosis among all workers. However, there was a 25 percent prevalence of silicosis among the 251 workers who had been employed for 5 or more years in the DE industry and who had had no prior occupational dust exposure. A nearly 50 percent prevalence of silicosis was detected radiographically among 101 workers employed in processes where the dust contained a high percent of cristobalite [Cooper and Cralley, 1958]. Subsequent x-ray surveys conducted at these plants indicated marked reductions in silicosis prevalence (e.g., 2.3 percentage by 1984), that appear to have paralleled reductions in dust exposure levels [Cooper and Jacobson, 1977; Cooper and Sargent, 1984].

In 1976, the National Institute for Occupational Safety and Health (NIOSH) conducted a health hazard evaluation at the Manville operation in Lompoc, California in response to workers' concerns about possible morbidity associated with dust exposure. In their survey, the NIOSH investigators [Okawa and Meyer, 1977] reviewed workers' death certificates and reported what they regarded as excessive frequencies of lung cancer and other respiratory disease mortality, although no supportive data were shown. The NIOSH report indicates that there were plans to conduct a complete epidemiologic study of this population; however, we are not aware of any such study having been performed.

To our knowledge, the study described in this report is the first formal epidemiologic study of mortality patterns among DE workers ever conducted.

CHAPTER II

REVIEW OF THE EPIDEMIOLOGIC LITERATURE ON SILICA AND LUNG CANCER

The possibility that crystalline silica may be a human carcinogen has been the subject of considerable interest and debate during the past ten years. Attention to this issue heightened following Goldsmith et al's 1982 review which suggested that the available scientific evidence supported a causal association. Other authors who have reviewed the medical literature subsequently reached different conclusions [Heppleston, 1985; McDonald, 1989]. Nevertheless, since Goldsmith's 1982 report, epidemiologic and experimental research on the carcinogenicity of crystalline silica has burgeoned. Most of the interest occurs because there are millions of workers worldwide who have been exposed previously or are currently exposed to crystalline silica in various industries. Lung cancer is the primary concern in the consideration of the potential carcinogenicity of crystalline silica because inhalation is the most toxicologically important route of exposure in humans.

This review provides a summary of some of the epidemiologic literature on this topic. The IARC [1987a,b] evaluations of both amorphous and crystalline silica include assessments of data from experimental studies on animals and epidemiologic studies of humans. This brief overview is limited to epidemiologic studies of occupational populations because data from these studies are most relevant to the present issue regarding risks among DE workers. We have not attempted to review the literature exhaustively. Instead, we have reviewed what we regard as pertinent literature published primarily during the past ten years. We attempted to review the most recent publications in instances where studies have been updated. We have further limited the review to occupational cohort studies and, in a few instances to proportionate mortality and case-control studies within occupational cohorts. Our view is that studies based on defined occupational cohorts provide the most meaningful information on effects. Thus, we have not included population-based case-control or census surveys in which silica and lung cancer associations have been examined because these studies generally are characterized by inadequate or nonexistent exposure data.

The occupational cohorts included in this review are: 1) certified silicotics, usually identified from diverse industries; 2) workers in industries with low potential for exposures to other suspected carcinogens (granite, slate quarry, refractory brick); and 3) industries with probable exposures to other suspected carcinogens (pottery and ceramics, metal mining, foundries). The main findings from the literature reviewed are summarized in Tables II.1-3. For each study, we present the lung cancer relative risk for the entire cohort, and the relative risk for the subset of workers with the "heaviest" crystalline silica exposures. The definition of the most heavily exposed varies from study to study. Where published information allowed, we designated the most heavily exposed as workers with the highest cumulative crystalline silica exposures. In most instances, however, surrogate indicators of cumulative exposure were used, such as duration of employment, time since first employment, or the presence of silicosis (assuming that these workers received the greatest exposures). The 'Comments' column of each table gives explanations for the definitions of most heavily exposed.

A. Silicotics

The largest group of studies was of silicotics certified in workers' compensation or equivalent disability award programs. Typically, members of these cohorts derive from multiple and diverse industries, although in some instances [Finkelstein et al., 1987; Carta et al., 1991; Chia et al., 1991] one or two industries were the predominant sources.

A review of the data in Table II.1 reveals consistently large lung cancer excesses, with most relative risk (RR) estimates greater than 2.0, which indicates at least a doubling of risk among silicotics compared to baseline rates (usually, national averages). Two of the overall lung cancer RRs exceed 5.0 [Merlo et al., 1990; Chiyotani et al., 1990], which indicate extraordinarily pronounced excesses.

Interpreting the data from cohort studies of silicotics is difficult for several reasons. First, these are not true cohorts in the epidemiologic sense of defined occupational groups whose health experience is tracked systematically over time. Also, most silicotic cohorts include workers from multiple industries; consequently, the studies provide no information on exposure levels. Exposures to crystalline silica may be inferred to be high, under the assumption that the silicotics represent the most heavily exposed workers from the source occupations and industries. However, the absence of crystalline silica measurement data precludes dose-response estimation (this situation is by no means unique to the cohort studies of silicotics). The absence of data on other potentially carcinogenic exposures (e.g., radon in underground mines) that may explain some of the lung cancer excesses is another limitation of these studies. Potentially the most vexing issue is the possibility that the studies of silicotics are biased from confounding by cigarette smoking. Thus, it has been suggested that smoking contributes to respiratory impairment among silicotics and thus increases the likelihood that silicosis patients will seek and receive compensation [McDonald, 1989]. However, in the absence of reliable data on smoking, arguments about confounding and other biases attributable to smoking are speculative.

B. Crystalline Silica-Exposed Cohorts with Unlikely Exposures to Other Suspected Carcinogens

1. Granite and Slate Industry Workers

Data from the five studies reviewed are summarized in Table II.2. These cohorts include workers involved in the mining, quarrying, crushing, and crafting (e.g., stone cutting) of granite and slate. Risks from silicosis in the granite industry have been recognized throughout this century, and the absence of obvious exposures to other carcinogens makes this a suitable group for study. The results in these studies are generally consistent, showing small to modest overall excesses (RRs ranging from 1.1 to 2.0). Somewhat higher relative risks among the most heavily exposed workers provide some indication of dose-response trends. In particular, the relative risk of 8.1 among Danish skilled sandstone workers, while based on only 7 lung cancer deaths, occurred in a craft that had experienced an approximately 50 percent prevalence of silicosis in past years [Guenel et al., 1989].

2. Refractory Brick Plant Workers

This industry manufactures silica bricks used in coke ovens, cast iron furnaces, and in glass and ceramic manufacturing. The Italian studies [Puntoni et al, 1988; Merlo et al., 1991] found modestly elevated lung cancer relative risks of 1.5 to 1.8 (Table II.2). A 1979 publication from the Soviet Union [Katsnelson and Mokronosova, 1979] reported a relative risk of 2.0 in this industry, but the study methodology was too sketchily described to be evaluated. Studies of refractory brick workers are especially pertinent to the DE industry because the manufacturing process also involves kilning of raw material, and the dust of the end product can contain a high free crystalline silica content (20-60 percent).

C. Crystalline Silica Exposed Cohorts with Probable Exposures to Other Suspected Carcinogens

1. Pottery and Ceramics Industries

Some operations in these industries may only involve crystalline silica exposures, whereas in others, fibrous and non-fibrous talc are potential confounding exposures. The overall lung cancer relative risks [Winter et al., 1990; Thomas, 1990] are similar in magnitude to those reported from studies of granite and stone workers. A strong apparent effect of concomitant exposure to non-fibrous talc was seen in the study by Thomas [1990] (Table II.3).

2. Metal Miners

Significant crystalline silica exposures can occur in underground metal mining, as evidenced by high prevalence rates of silicosis in past years. The lung cancer hazards posed by radon progeny in underground mining are well documented [National Research Council, 1988]; thus, radon should be regarded as a potential confounder for the relationship between crystalline silica and lung cancer. For this reason, we did not include studies of uranium miners in this review. Other occupational exposures that may be confounders in mining environments include the mined metals and their oxide forms, other metal contaminants in the ores (e.g., arsenic), diesel exhausts, and amphibole fibers (e.g, cumington-grunerite).

The studies listed in Table II.3 provide mixed results. Brown et al. [1986] reported no excess of lung cancer among the Homestake mine workers in South Dakota. In contrast, Hnizdo and Sluis-Cremer's [1990] analysis of the South African gold miner cohort data suggests a strong dose-response relationship. However, interpreting the data from this most recent publication on the South Africa gold miners study is complicated by conflicting previous reports regarding the association of lung cancer with crystalline silica published by the same group of investigators [Wyndham et al., 1986; Hessel et al., 1986; Hessel et al., 1990]. The main consistent finding from these publications is an apparent lack of association between parenchymal silicosis and lung cancer.

Amandus and Costello [1991], in their study of U.S. non-uranium metal miners, observed a small excess (RR=1.2) in the entire cohort, and a somewhat stronger association among the identified silicotics (RR=1.73). The excess among silicotics is not as large as those found in most of the studies of certified silicotics (Table II.1). Although uranium miners were not included in this study, some effect of radon cannot be completely discounted. The study of hematite miners in China [Chen et al., 1990] demonstrated a pronounced lung cancer excess (RR=3.7); however, the authors point out that the independent effects of crystalline silica and radon progeny cannot be distinguished clearly because of correlations between the two exposures. Hodgson and Jones [1990] detected an excess of lung cancer risk among U.K. tin miners, with the largest excess concentrated among workers with 30 or more years of underground mining experience (RR=4.5). However, confounding from radon and arsenic could not be discounted in this study.

3. Foundries

Foundry environments are complex mixtures of dusts and chemicals. Excessive exposures to crystalline silica have been documented in some instances [e.g., Silverstein et al., 1986], yet other agents, especially carcinogenic polycyclic aromatic hydrocarbons, such as benzo(a)pyrene, also are potential lung carcinogens [Palmer and Scott, 1981; Gibson et al., 1983]. Relatively modest excesses of lung cancer have been seen in a number of foundry cohorts (Table II.3), and the evidence for a specific association with crystalline silica is weak. A relative risk of 1.7 among silicotics in the Danish study [Sherson et al., 1991] provides the strongest support for a unique effect of crystalline silica dust.

D. Summary

Several possible mechanisms of crystalline silica-induced lung carcinogenesis have been suggested: 1) crystalline silica may act as a cancer initiator, thus directly causing cancer; 2) silicosis may be an intervening pathogenetic step that ultimately leads to lung cancer; or 3) crystalline silica may be a co-factor that acts synergistically with other carcinogens, such as cigarette smoke or radon progeny [Goldsmith et al., 1982]. These mechanisms are not necessarily mutually exclusive, as the true effect of crystalline silica may be some combination of these pathways. It should be appreciated that, whereas epidemiologic studies offer the most pertinent qualitative and quantitative information on risks associated with environmental exposures, they are generally of limited assistance in elucidating pathogenetic mechanisms.

In reviewing the literature, it becomes quite evident that the lung cancer associations are substantially stronger among certified silicotics than among non-silicotic exposed workers. There are several possible explanations for this observation. The simplest is that silicotics may be the most heavily exposed workers, and the concentration of excess among this group reflects an underlying dose-response relationship between crystalline silica and lung cancer. It may be that pulmonary fibrosis is a predisposing or intermediate factor in lung carcinogenesis, as suggested by data on asbestos-exposed workers [Hughes and Weill, 1991]. However, differences in the pathological nature of the fibroses caused by asbestos and crystalline silica may make analogies between the two inappropriate [Heppleston, 1985]. Another possibility is that the studies of certified silicotics are biased by selection factors. Thus, as mentioned previously, these cohorts may be over-represented with smokers whose lung cancer risks are expected to be excessive. The absence of data on smoking in the silicotic cohort studies, and in most of the other epidemiologic studies of crystalline silica-exposed workers, limits interpretation of the results.

The studies of granite, stone, and brick plant workers are in certain respects most relevant to considerations about the possible carcinogenic effects of diatomaceous earth. Crystalline silica exposure is the main environmental hazard in these industries; for the most part, these cohorts were not exposed to other known or suspected lung carcinogens. In contrast, the interpretation of the data from the miners and foundry studies is clouded by the possibility of confounding from other occupational lung carcinogens. The excesses have not been large in most of the studies of stone, granite, and brick workers, although some suggest the possibility of dose-response relationships.

As with the studies of silicotics, absence of data on smoking is a pervasive limitation. Of course, the main shortcoming of most of the literature is the lack of data on exposure levels that would permit quantitative dose-response estimation. Duration of employment in the industry, which is often used as a dose surrogate, is fraught with uncertainty because workers who may actually have accumulated very large doses during short time intervals are not identifiable when the analysis relies merely on tenure in the industry. The net effect is that dose-response relationships, if present, will be underestimated or go undetected. Silicosis may be used as an indicator of high dose, assuming that silicosis itself is necessarily dose-dependent. However, the identification of silicotics was probably not systematic or complete in some industries. Moreover, inter-individual differences in fibrogenic response to crystalline silica may undermine the validity of silicosis as a dose marker.

Despite the limitations of the available epidemiologic evidence, the consistency of the findings suggests a causal contribution of occupational crystalline silica exposure to lung cancer risk. However, it is not strictly appropriate to extrapolate results from previous investigations to the DE industry because of differences in the types of silica exposure. In particular, most of the published epidemiologic literature pertains to quartz, whereas cristobalite and amorphous silica are the principal DE silica exposures. Differences in carcinogenic potential for the various forms of silica may exist. Furthermore, dissimilarities in study design and methods of exposure assessment and data analysis between the present study and previous investigations also are arguments against extrapolation. Thus, we view the findings from this study as relevant primarily to the DE industry, and more specifically to the worker populations included in the analysis.

Table II.1
Lung Cancer Among Cohorts of Certified Silicotics

Author (year)	Location	Size of cohort (workers)	Results for: Entire cohort RR†	(No. cases)	Most heavily exposed‡ RR†	(No. cases)	Comments
Schuler (1986)	Switzerland	2,339	2.23	(180)	—	—	
Westerholm (1986)	Sweden	712	3.47	(17)	—	—	Mines, quarries, tunneling
Zambon (1987)	Italy	1,313	2.39	(70)	2.56	(15)	Highest: >20 yr exposure
Finkelstein (1987)	Ontario	1,479	2.42	(78)	—	—	Surface & underground miners
Infante-Rivard (1989)	Quebec	1,165	3.47	(83)	3.62	(39)	Highest: >30 yr employment
Forastiere (1989)	Italy	595	1.50	(64)	—	—	Proportionate mortality study
Merlo (1990)	Italy	520	6.85	(26)	—	—	
Ng (1990)	Hong Kong	1,419	2.03	(28)	6.75	(7)	Highest: category "C" silicosis
Hessel (1990)	S. Africa	231	—	—	1.21	(39)	Case-control (nested) highest: cumulative exposure index
Chiyotani (1990)	Japan	1,941	6.03	(44)	—	—	RR=2.22 (4 obs) in non-smokers
Tornling (1990)	Sweden	280	1.88	(9)	2.36	(9)	Highest: >10 yr after diagnosis
Chia (1991)	Singapore	159	2.01	(9)	2.54	(5)	Incidence study; highest: >40 yr employed
Carta (1991)	Sardinia	724	1.29	(22)	1.54	(4)	Mostly mines & quarries; highest: cumulative exposure index
Amandus (1991)	N. Carolina	760	2.36	(34)	4.5	(7)	Highest: also exposed to other carcinogens (e.g. asbestos)

† Relative risk estimate
‡ Workers with highest silica exposures, defined in various ways (see Comments)

Table II.2
Lung Cancer Among Crystalline Silica-Exposed Occupational Cohorts with Low Potential for Exposure to Other Suspected Carcinogens

Industry, Author (year)	Location	Size of cohort (workers)	Results for: Entire cohort RR†	(No. cases)	Most heavily exposed‡ RR†	(No. cases)	Comments
Granite							
Steenland (1986)	U.S.	1,905	1.19	(97)	1.08	(49)	Proportionate mortality study; highest: ≥20 yr in Granite Cutters Union
Costello (1988)	Vermont	5,414	1.16	(118)	1.82	(47)	Highest: employed before 1940 and ≥ 30 yr employed and ≥ 40 yr since first employment
Mehnert (1990)	Germany	2,483	1.09	(27)	1.57	(17)	Highest: employed ≥ 20 yr
Koskela (1990)	Finland	1,026	1.56	(31)	2.26	(7)	Highest: ≥ 30 yr since first employment
Guenel (1989)	Denmark	2,071	2.00	(44)	8.08	(7)	Incidence study; highest: skilled sandstone workers
Refractory brick							
Puntoni (1988)	Italy	231	1.83	(11)	—	—	
Merlo (1991)	Italy	1,022	1.51	(28)	2.01	(13)	Highest: ≥ 20 yr since first employment

† Relative risk

‡ Workers with highest silica exposures, defined in various ways (see comments)

Table II.3

Lung Cancer Among Crystalline Silica-Exposed Cohorts with Probable Exposures to Other Suspected Carcinogens

Industry Author (year)	Location	Size of cohort (workers)	Results for: Entire cohort RR†	(No. cases)	Most heavily exposed‡ RR†	(No. cases)	Comments
Pottery and Ceramics							
Winter (1990)	England	6,187	1.34	(60)	1.51	(21)	Smoking-adjusted RRs; highest: ≥1.50 mg/M^3 x yr
Thomas (1990)	U.S.	2,055	1.43	(52)	3.64	(8)	RR = 1.37 (18 obs) among no talc exposure group; highest: ≥ 15 yr employed also exposed to non-fibrous talc
Metal miners							
Brown (1986)	S. Dakota	3,328	1.00	(43)	0.60	(2)	Gold mine; highest: cumulative dust exposure index
Chen (1990)	China	5,406	3.69	(29)	4.80	(12)	Hematite mine; highest: silicotics with heaviest exposures
Hodgson (1990)	U.K.	3,010	1.58	(105)	4.47	(15)	Tin mines; highest: >30yr underground mining
Hnizdo (1991)	S. Africa	2,209	—	—	2.92	(23)	Gold mine; highest: based on categories of particle-yr (1000) (> 40 vs. ≤ 15)
Amandus (1991)	U.S.	9,912	1.18	(118)	1.73	(14)	Copper, zinc, lead, mercury and other non-uranium mines; highest: silicotics

Table II.3 (cont'd.)

Industry, Author (year)	Location	Size of cohort (workers)	Results for: Entire cohort RR†	(No. cases)	Most heavily exposed‡ RR†	(No. cases)	Comments
Foundries							
Decoufle (1979)	U.S.	2,861	1.26	(29)	1.28	(12)	Gray iron foundry; highest: employed ≥ 5 yr
Egan-Baum (1981)	U.S.	3,013	1.48	(263)	—	—	Proportionate mortality study of molders union members
Fletcher (1984)	England	10,250	1.48	(2.96)	—	—	Steel foundry
Silverstein (1986)	U.S.	278	1.38	(31)	—	—	Gray iron foundry; proportionate mortality study
Sorahan (1989)	U.K.	10,491	1.47	(441)	—	—	Steel foundry
Sherson (1991)	Denmark	6,144	1.30	(166)	1.71	(11)	Iron and other metal foundries; highest: silicotics

† Relative risk

‡ Workers with highest silica exposures, defined in various ways (see Comments)

CHAPTER III

MATERIALS AND METHODS

This chapter provides descriptions of the study design and the sources of data used to enumerate and trace the study population, to assess exposures, and to perform the data analyses.

A. Descriptions of the Plants Studied

Diatomaceous earth is generally extracted by open pit or quarry mining. The raw DE is then crushed, dried, and sorted to remove contaminants. The material may then be calcined by heating in a kiln at temperatures ranging from 800 to 1000^{o}C. Sodium carbonate (soda ash) or sodium chloride may also be added as a flux. The natural, calcined, or flux-calcined product is then classified by size, and either bagged or loaded into bulk containers.

DE mining and processing operations of four companies were considered for inclusion in the study. By far the largest and oldest of these operations is the Lompoc, California mine and mill owned until recently by the Johns-Manville Corporation. DE was discovered in the Lompoc area in the late 1800s, and mining operations began in 1902. The site of the original mine and milling operations was bought by Johns-Manville in 1928. The operations continue to this day to produce natural, calcined, and flux-calcined materials, as well as "silicate," a material composed of DE and lime.

Another mining operation in Lompoc was started in 1946 by the Great Lakes Carbon Company, and a mill was opened in 1952. The company ceased mining directly and began contracting out its mining operation in the late 1950s. Although the plant originally produced some natural materials, since the 1960s only calcined and flux-calcined DE have been produced. Grefco Inc. has owned and operated this plant since 1966.

Grefco also owns a second, smaller mine and mill operation in Basalt, Nevada which only processes natural DE products. The Basalt plant was opened in 1929 by the Dicalite Company, and was operated by the Great Lakes Carbon Co. from the 1940s until 1966.

Eagle-Picher Minerals has operated two DE processing facilities in Nevada, one since the mid 1940s, and a second since the late 1950s. One plant produces both natural (dried) and calcined absorbent products and the other plant produces calcined and flux-calcined filter aids.

The smallest plant is the Witco Corporation facility in Quincy, Washington. DE handling has taken place in Quincy since 1910 when the operation was a burlap sack bagging process. Mining operations began in 1935, and calcining and flux-calcining started in 1947. The plant was bought by the Witco Corp. in 1970, and, personnel and industrial hygiene data are only available since that time.

B. Study Design

The historical cohort design was used in this investigation. In brief, this study design involves the enumeration of a cohort of workers employed during past years, and observations of the exposure and health experience of the cohort over time, starting with past years and proceeding forward to the present. The study population included workers who were employed in the DE industry for a minimum of 12 months cumulative service prior to 1 January, 1988. The restriction of the cohort to workers employed for at least 12 months was imposed to avoid including workers whose exposures were probably too brief for a meaningful analysis of work-related health outcomes. Also, vital status tracing in epidemiologic studies of short-term workers typically is less complete than for longer-term workers. We used a dynamic cohort definition which permitted workers to be eligible for inclusion irrespective of date of first employment, provided that they met the inclusion requirements just mentioned. The dynamic cohort design allows more subjects to be included in a study than a fixed cohort of workers employed as of a single point in time, and thus increases statistical precision of effect estimates [Checkoway et al., 1989].

C. Cohort Enumeration

1. Lompoc Workers

The Lompoc cohort includes workers at the Grefco and Manville diatomaceous earth production facilities in Lompoc, CA. The personnel data for the Manville and Grefco plants were reviewed and appeared to be well maintained with no obvious indications that there were systematic inconsistencies in data quality or completeness.

Manville maintained separate record systems for workers' personnel and medical files. All employees were required to have medical records that included pre- and post-employment examination data (including chest radiograph findings). Thus, the medical records provided a convenient check on the completeness of the personnel files. January 1, 1942 was chosen as the cohort inception date because this was the earliest date for which seemingly complete personnel data could be assembled. The Grefco plant opened in 1952; thus, all Grefco employees who worked for at least 12 months cumulative service prior to January 1, 1988 were eligible for cohort inclusion.

A three phase approach was followed for enumerating the cohort. Details of the procedures are described below. Table III.1 presents a summary of the criteria used in each phase and the number of workers identified.

In Phase 1, all personnel records, irrespective of employment duration, were assembled. The data contained in each personnel folder were entered into a computer data base by temporary clerks who were trained and supervised by company personnel and the UW investigators. Initially, the file of all potentially eligible cohort members was limited to the minimally required data items: full name, gender, race, date of birth, social security number, date of first hire, and date of last employment. Totals of 12,759 Manville and 613 Grefco employees were identified at this stage. A check of the Manville medical records revealed that 61 (less than 0.5 percent) workers were not identified from personnel files. These workers were not included in the cohort because the corresponding personnel data could not be located. For each worker a crude employment duration was estimated as the difference between last employment date and hire date.

In Phase 2 of cohort enumeration we eliminated workers whose crude service dates were less than 365 days and workers whose last employment dates were before January 1, 1942. Personnel files for the remaining workers were then reviewed in detail for employment history information. The complete work history data were then entered into computer files. The work history data that were computerized included job codes, dates of and reasons for job changes (including temporary assignments), layoffs, leaves of absence, and employment termination dates.

Phase 3 involved an in-depth review of work histories and selection of the final study cohort. Birth dates, dates of first hire, dates of last employment, and the aforementioned work history data were combined and reviewed for consistency. A detailed review of the original data source was conducted whenever a work history overlapped hire or last employment dates, or whenever a long gap in work history between first and last dates of service was detected in the computerized data file. After a work history was considered to be complete and accurate, it was re-examined to confirm that the worker had been actively employed (excluding layoffs and leaves of absence) for 365 days; workers who satisfied this requirement were included in the study cohort.

There were 33 Manville workers with missing or seriously incomplete work history records, and 9 Grefco employees with either missing dates of birth or missing work history records. These workers were not included in the cohort.

A small number of jobs at Manville and Grefco were identified by company personnel as having had the potential for asbestos exposure. Also, several Manville workers had transferred from other Manville plants where asbestos was used or processed. Based on this information, 104 employees (all white males) were identified as having the potential for occupational asbestos exposure. These 104 workers include 97 from Manville and 7 from Grefco; none had transferred between the two plants.

At the completion of Phase 3, we had identified 2,961 workers who met eligibility criteria, including: 2,674 white males; 37 black males; 242 white females; and 8 black females. The main analysis cohort was defined as 2,570 white males without known occupational asbestos exposures. Data for the other groups, 104 asbestos-exposed white males, black males, and white females, were analyzed separately. The number of black female workers was considered too small to support a meaningful analysis of mortality.

2. Other Plants

Cohort enumeration for the Basalt and Witco plants involved the same three phase procedure followed for the Lompoc workers. For Basalt, the Phase 1 collection identified 673 workers, of whom 158 (all white males) met cohort eligibility criteria and for whom there was adequate demographic and work history information. The final Witco cohort includes 121 workers, all white males.

The personnel records for the two Eagle-Picher plants were too incomplete to permit cohort enumeration. In some instances these data were missing dates of employment and lack of detail on jobs held at the plants. Furthermore, during a subsequent visit to the Eagle-Picher office, we discovered file drawers of personnel folders that were not previously entered during the Phase 1 data collection. Consequently, we have not included data for the Eagle-Picher workers in this report. Ultimately, a cohort reconstruction for this company may require compilation of Internal Revenue Service quarterly earnings reports [Marsh and Enterline, 1979].

D. Vital Status Follow-up

Vital status tracing was performed for the years 1942-87, inclusive. Ordinarily, the Social Security Administration (SSA) is the primary source of vital status information in occupational cohort mortality studies. SSA had ceased to offer vital status tracing services at the time this study was conducted. Consequently, other data sources were used to determine vital status for workers who were not actively employed as of the end of follow-up (31 December, 1987). These sources include: SSA death tapes made available through Pension Benefits Info., Co. of San Francisco; the California Automated Mortality Linkage System (CAMLIS); California death records; motor vehicles bureaus for California and Nevada; and two credit bureau searching companies, CSC and Trans Union. CAMLIS is a sophisticated computer search system that matches social security number, name, date of birth, and date of death (if known) with all deaths that occurred in California since 1960 [Arellano et al., 1984]. In addition, we conducted a search of the National Death Index (NDI) which is a computerized data base of all deaths that occurred in the U.S. since 1979.

Living status was inferred from motor vehicles and credit bureau records if there was evidence of a transaction that took place after December 31, 1987 (e.g., driver's license renewal, or credit transaction). Because the NDI has virtually complete mortality information [Acquavela et al., 1986], any person who had left employment or was identified as alive by motor vehicle or credit bureau records after 1 January, 1979, but was not identified from the NDI search, was assumed to be alive as of the end date of follow-up. Individuals who were lost to follow-up prior to 1979 were considered alive until the later of date of last employment, driver's license renewal, or credit transaction (identified by CSC or Trans Union).

E. Cause of Death Determination

Copies of death certificates were requested and obtained from the vital statistics offices of the states where the deaths occurred. The companies provided copies of death certificates for 30 deaths that they had already collected for other purposes. These 30 deaths were subsequently confirmed by other sources. All death certificates were coded by a trained nosologist according to the International Classification of Diseases (ICD) codes in effect at the times when the deaths occurred. This involved using codes for the 5th through the 9th revisions of the ICD.

F. Exposure Assessment

Although the mining of raw DE and its subsequent conversion into commercial products is a relatively simple process, the assignment of exposures to jobs was not. An individual's exposure to crystalline or amorphous silica may vary on the basis of the type of product handled (natural, calcined, or flux-calcined), the duties of the job, and the percentage of respirable dust. In addition, factors that have changed over time, such as the use of personal protective equipment, the effectiveness of engineering controls, and house-keeping practices have had a major influence on reducing exposures.

The procedures used to assess exposure that are described in this section pertain to the Lompoc plants. Exposure assessment for the Witco and Basalt plants was limited to estimating employment duration because of the small cohort sizes.

1. Description of Sources of Information

In order to assess exposures, information from a number of sources was used. First, with the help of company personnel, detailed work history information was collected for all workers employed for one year or more of cumulative service in the industry. The information collected included the job title and the start and end dates for each position held by each employee. Next, interviews with company personnel and extensive tours of company facilities were conducted in order to familiarize the investigators with the duties and potential for exposure in each job. Additionally, industrial hygiene sampling data, published government documents, and articles from the scientific literature were reviewed for relevant exposure information.

2. Industrial Hygiene Data

Industrial hygiene sampling methods for dust have changed over time. Before the 1970s, samples were collected by the "impinger" method which gives dust concentrations in units of millions of particles per cubic foot (mppcf). In more recent years, dust samples have been collected using filters, from which total dust is measured in units of milligrams per cubic meter (mg/M^3). When an additional device known as a cyclone is used, respirable dust can also be determined. In order to convert the results of industrial hygiene sampling using the older method into newer units, side-by-side measurements were taken to develop conversion factors

[Montgomery et al. 1991]. Conversion factors were developed for exposure to the regular commercial product, such as might happen at a packing station, and for DE exposure in baghouses, which has a higher respirable content.

All available industrial hygiene sampling data were requested from each of the companies. Manville supplied the results for over 5,500 dust samples taken between 1962 and 1988. Grefco provided graphs and survey sheets which summarized the results of over 2,500 dust samples taken at their Lompoc plant between 1952 and 1988. Both companies provided area and personal sampling data.

There were several difficulties encountered in our efforts to assign exposure levels to each job using the industrial hygiene data. The highest exposures among the study population occurred prior to 1954 at the Manville plant; therefore, the lack of industrial hygiene sampling data for the earlier time periods severely limits the utility of the data for estimating quantitative exposure levels. Many jobs and processes had been discontinued or had undergone drastic changes prior to 1962, the earliest date for which sampling results from Manville were available.

In addition, data were not available for many jobs, while very few samples were taken for others. Furthermore, many of the samples were taken to determine the dust levels in particular areas, and it is unclear to what extent they were representative of workers' actual exposures. For example, area samples taken in warehouses may not represent the exposures experienced by warehouse workers because dust may settle until disturbed by a fork-lift or other work activity. Finally, even many personal samples may not necessarily be representative of the average exposures of a worker in a particular job. Some samples were taken during a particular activity which may be only one of many assigned to that individual; consequently, it was difficult to determine an average daily exposure for that worker. Given these limitations, industrial hygiene sampling data were used primarily to help verify the relative exposure classifications (i.e., "high" vs. "intermediate" vs. "low") for selected jobs for which the sampling data appeared to be representative. This information was also used to some extent to help determine the weighting of the high, intermediate, and low exposure classifications.

3. Exposure Characterization

a. Level of Dust Exposure

In order to assess the level of dust exposures, each job was classified according to a number of factors. First, each job was assigned a relative ranking for the intensity of DE dust exposure, i.e., none, low, intermediate, or high. The levels were then assigned weighting factors such that cumulative exposure could be estimated. In order to account for changes over time, exposures were further weighted to reflect the relative level of exposure in the time periods in which they occurred. Finally, a respirator protection factor, which changed over time, was assigned in order to reflect the increasing use of respirators in the industry. Each of these steps will be described in detail below.

First, the work histories were summarized by combining jobs with similar work duties and exposures into homogeneous groupings of job titles. Because there was inadequate information available for a quantitative assignment of exposure intensity levels, a four-point qualitative dust exposure scale (none, low, intermediate, high) was devised. Assignment of exposure level was based primarily on the assessments of two of the investigators (PD and NH), both industrial hygienists, after extensive consultation with senior health and safety personnel from the industry. The results of industrial hygiene samples were also taken into consideration. The jobs and their classification by intensity of exposure and product type are listed in Appendix A.

Office workers, security guards, medical personnel, gardeners, and cooks were assigned to the "no exposure" category. Although, dust exposure occurs in the environment around the plant, exposures to workers assigned to these areas were judged to be negligible relative to mine and mill workers' exposures. The "low" exposure category consists primarily of supervisory and engineering personnel who spend the majority of their time in unexposed environments (e.g., offices), lab workers, and workers whose duties placed them primarily in an enclosed control room. The "low" exposure category also includes maintenance workers who performed all of their duties in shops located away from the production process or outside the plant in a relatively unexposed area.

The "high" exposure category includes packers, baghouse workers, re-feeder workers, mill janitors, high level cleaners, dust leak patchers, sackroom workers (where burlap bags were reclaimed), warehouse workers, and lift truck drivers. Because of their job duties, these workers had the greatest opportunity for exposure and have traditionally been considered to be the most heavily exposed. The "intermediate" exposure category includes all other mill jobs, as well as almost all quarry jobs. This category includes many of the skilled trades workers because much of the repair and maintenance work was performed on the shop floor; thus, workers in these jobs probably experienced intermittently high and low exposures.

An exposure intensity weighting scheme was developed to facilitate the examination of mortality risks in relation to levels of cumulative exposure. Work in unexposed jobs was assigned a value of 0, work in lightly exposed jobs was assigned a value of 1, and work in intermediately and highly exposed jobs were assigned weights of 3 and 6, respectively. Examples of representative industrial hygiene sampling results from the Manville plant are given in Table III.2.

Over the decades, dust exposures have decreased dramatically in the DE industry. Early in the development of the industry exposures were quite high. An early attempt to decrease exposure at the Manville facility was the exhausting of DE dust not captured by the cyclones into an old tunnel in an adjacent hill, thus decreasing ambient dust levels in that area of the plant and in the area close to housing for some of the workers. Technology began to change in the industry during the 1940s, and after World War II increased attention was paid to dust control. Paper bags replaced burlap for the packaging of diatomaceous earth, hand trucks were replaced by lift trucks and pallets, and dust collectors and vacuum cleaners were installed in many areas of the plant for dust control.

In 1952, the International Chemical Workers Union began a strike at the Manville facility, with health protection being a major issue [Abrams, 1954]. In that same year the California State Department of Public Health requested that the U.S. Public Health Service (PHS) perform a medical and environmental exposure study of the industry [Cooper and Cralley, 1958]. The PHS investigators reported that exposures may have been several-fold higher in earlier years before the survey. In the aftermath of these events, concerted efforts were taken to reduce exposures, including the installation of ventilating baghouses and filter units on most quarry equipment. By 1955, the conversion from hand bag to mechanical unit loading had been completed for all products. The PHS surveys found substantial reductions in exposures from reported values of earlier years. For example, whereas 62% of the samples taken in the earliest (1953-54) survey were measured at 5 mppcf or higher, only 21% taken in 1956 were that high. The PHS investigators cited increased respirator use and improvements in housekeeping during this period, as well as increased local ventilation, use of "blow-off booths" for people and equipment, use of vacuums rather than compressed air hoses for cleaning, and the introduction of filtered air in the cabs of quarry vehicles as contributing factors in dust control.

Since the mid-1950s, there have been continued gradual improvements in exposure control in the industry. For example, in the 1960s the use of bulk cartons and the shipment of palletized products enclosed in plastic were introduced. The introduction of automation, such as the automatic packing system introduced at Manville in 1981, has further reduced exposures.

In an attempt to reflect some of the changes that have occurred over time, we divided the work histories into five time periods; prior to 1944, 1944 through 1953, 1954 through 1963, 1964 through 1973, and 1974 through 1987. We then assigned exposure weightings of 12, 6, 2, 1.5 and 1 to the five time periods to reflect the high exposures during the early years of the industry, the major attempts to control exposures between World War II and the final PHS surveys, and the gradual improvements in the control of exposure since that time.

Finally, an additional factor was introduced to reflect the use of respirators. Respirator use for workers in almost all high and intermediate exposure jobs has been required since the mid-1950s. Although enforcement and the quality of respirator programs was poor during the earlier decades, respirator use has increased over time. Respiratory protection factors of 0.8, 0.5, and 0.2 were assigned for the time periods of 1954 through 1963, 1964 through 1973, and 1974 through 1987, respectively. These factors were applied to the exposures above those received by the "low" exposed workers, which were considered to reflect the baseline, or ambient, conditions in the plant. The factors representing the estimated effects of intensity of exposure, changes over time, and use of respiratory protection are presented in Table III.3. The index of cumulative weighted dust exposure was then obtained by applying the weights in Table III.3 to the work history data, and summing the products of the exposure weights and the corresponding durations in days for each cohort member.

b. Exposure to Crystalline Silica

Each job was classified according to type of product handled in order to permit examination of risks associated with estimated crystalline silica exposure. Quarry jobs and other jobs that involved working with DE prior to calcination were classified as only exposed to "natural" products. The Manville plant has produced a number of non-calcined DE products. Accordingly, jobs in the areas of the plant that process and pack those products were also assigned to the "natural" exposure category. The silicate plant is a separate building on the Manville site that produces a product composed of natural DE, lime, and a small amount of flux-calcined product. All silicate plant workers, with the exception of those responsible for adding and mixing the flux-calcined DE, were assigned to the "natural" products category.

Almost all other jobs involved exposure to multiple types of DE products. For example, powder mill workers at Manville work with a combination of both calcined and flux-calcined products, while many other Manville employees, such as warehouse and maintenance workers, are exposed to "natural" as well as calcined products. In addition, the relative percentages of product types have changed over time and have differed between the two companies.

Company representatives provided the investigators with estimates of the proportions of the various DE materials (natural, calcined, and flux-calcined) produced at different times, as well as estimates of the percentages of crystalline silica present in the respirable fractions of the three dust types. It was estimated that only 1% of "natural" DE is crystalline silica. The crystalline silica content of calcined and flux-calcined DE was felt to differ between the two companies with plants in Lompoc. At the Manville plant the factors were 10% and 20% for calcined and flux-calcined DE respectively, whereas at Grefco the corresponding numbers were estimated to be 20% and 25%. The crystalline silica percentages were assumed not to have varied over time.

Estimates of workers' cumulative exposures to crystalline silica were obtained by applying weights for the percentages of the various product types handled in each job at various time periods, and the corresponding percentages of crystalline silica in the dust, to the weighted dust exposures derived using the weights from Table III.3.

G. Methods of Data Analysis

1. Lompoc Cohort: White Males

Data analysis for the Lompoc white males, who comprised the largest group, consisted of two general phases. The first set of analyses involved comparisons of cause-specific mortality rates between the cohort and the national and regional (i.e., external) reference populations of white males. For each cause of death, we estimated relative risks by computing Standardized Mortality Ratios (SMRs). The SMR is the ratio of the observed number of deaths from a particular disease or disease category to the number expected, based on rates in the reference population. Expected numbers are derived by multiplying the reference rates for 5-year age and 5-year calendar periods by the corresponding numbers of person-years in the cohort. The expected number of deaths for a given disease is obtained by summing the age/calendar year-specific expected numbers. An SMR equal to 1.0 indicates neither an excess nor a deficit of mortality from that disease, whereas an SMR greater than 1.0 suggests an excess, and an SMR less than 1.0 suggests a mortality deficit.

In the SMR analyses, person-time counting for each worker started at either 1 Jan. 1942 or the date when 365 days of cumulative service was achieved, whichever occurred later. Workers contributed person-years of observation up to the dates of death or 31 Dec. 1987, which ever occurred earlier. Workers with unknown vital status contributed person-time up to the dates when they were last known alive. SMRs were computed using the microcomputer version of the Occupational Mortality Analysis Program (OCMAP) developed by the University of Pittsburgh [Marsh and Preininger, 1980]. Expected numbers of deaths were based on national mortality rates obtained from the U.S. National Institute for Occupational Safety and Health (NIOSH). These rates are available for the years 1940 through 1988 for 92 separate cause of death categories [Steenland et al., 1990]. In order to control for regional differences in cancer risk, expected numbers were also obtained based on 1950-87 reference rates for Southern California (excluding the urban counties around Los Angeles and San Diego), and the four county area in which Lompoc is located. The county mortality rates were obtained from the University of Pittsburgh.

The second set of analyses involved comparing cause-specific mortality rates between subgroups of the Lompoc cohort, classified with respect to employment duration and the various indices of exposure (i.e., internal comparisons). Thus, these analyses were conducted to evaluate dose-response relationships. The analysis required computing person-time strata of age (<45, 45-49, 49-54...≥80), calendar year (<1955, 1955-59..., 1980-84, 1985-87), duration of follow-up (<10, 10-19, ≥20 yr), and strata determined by the exposure variables, using a special FoxPro Version 2.0 [Fox Software, 1991] person-year program developed for this purpose by one of the investigators (NH). These results were confirmed independently using the OCMAP program. Thus, each cohort member contributed person-time into each stratum attained. Age, calendar year, and follow-up duration were regarded as possible confounders because each is potentially associated with both disease risk and cumulative exposure [Pearce et al., 1986].

Mortality rate comparisons were made among subgroups of the Lompoc white male cohort classified with respect to the following exposure indices:

1) Total duration of employment in DE industry jobs (Strata: 1-4; 5-9; 10-19; ≥20 years)

2) Duration of employment in "dust-exposed" DE jobs (i.e., at least low exposure; Strata: < 5; 5-9; 10-19; ≥20 years)

3) Duration of employment in dust-exposed jobs, weighted with respect to job-specific differences in exposure level, temporal changes in dust exposure levels, and use of respiratory equipment, using the exposure factors in Table III.3 (Strata: < 50; 50-99; 100-199; ≥200; the stratum boundaries were set by multiplying the cohort's mean annual exposure intensity score (10) by 5, 10, and 20, corresponding to the duration of employment stratum boundaries used in (#1) and (#2) above)

4) Estimated cumulative exposure to crystalline silica, calculated by multiplying the weighted dust exposure (#3) by the percentage of crystalline silica in the various product mixes (Strata: 1-49; 50-99; 100-199; ≥200).

Relative risks, adjusted for age, calendar year, and duration of follow-up, and associated 95 percent confidence intervals for each exposure level were computed using Poisson regression modeling [Breslow and Day, 1987]. In each analysis, the relative risk for the lowest exposure category (e.g., 1-4 yr employment duration) was defined as 1.0, and the relative risks for the higher categories were expressed in reference to the lowest category. Poisson regression analyses were performed using EGRET [SERC, 1990], with person-years data generated from the FoxPro program mentioned previously.

It was of interest to evaluate the separate effects on disease risk of calcined and natural DE. However, as can be seen from Table III.4, only 5 percent (129) of the cohort had only worked in jobs with natural dust exposures. This small number thus precluded meaningful analyses of risks among workers only exposed to one or the other type of DE.

In the internal rate comparisons disease latency was taken into account by lagging exposures by the assumed latency interval [Checkoway et al., 1990]. To illustrate the method, consider a worker who had accumulated 8 years of employment in dust-exposed jobs by age 47 in 1956. If it is assumed that the disease in question (e.g., lung cancer) has a 5-yr latency interval (i.e., the time period between disease induction and detection, in this case death), then one would want to eliminate from consideration exposures that occurred within the preceding 5 years. Thus, the person-year for this hypothetical worker at age 47 in 1956 would be assigned an exposure value of 3, which is the duration of dust exposure accumulated 5 years previously. Thus, latency analysis of this type assigns each person-year of a worker's experience to the exposure value accumulated through the year immediately preceding the estimated latency interval. Exposure lags of 0, 5, and 15 years were used in each analysis.

2. Other Cohorts

Separate analyses were performed for the following groups of workers: 1) white males potentially exposed to asbestos at the Lompoc plants (N=104); 2) black males employed at the Lompoc plants (N=37); 3) white females at the Lompoc plants (N=242); 4) Basalt, Nevada plant workers (all white males; N=158); and 5) Quincy, Washington plant workers (all white males; N=121). Because of the small sizes of these cohorts, the analyses were limited to SMR comparisons against the U.S. population for selected causes of death.

3. Presentation of Data

We should point out that, in the presentation of the results, no reference is made to statistical significance (i.e., p-values). Likewise, the discussion of the results does not include a consideration of statistical significance. Instead, we prefer to present results (i.e., relative risk estimates) with their associated confidence intervals which give an indication of the statistical precision of the findings. Thus, a wide confidence interval indicates numerical imprecision (statistical instability) due to small numbers, whereas a narrow confidence interval suggests the opposite. The reader who feels compelled to place the findings in the context of "significant" or "not significant" can infer this information by the inclusion or exclusion of the no effect value for the relative risk in the confidence interval. Thus, for example, a relative risk of 1.6, with a 95 percent confidence interval of 1.2-2.8, may be regarded as statistically significant at the 5-percent probability level, although in our view, more meaningful inference is obtained by evaluating the magnitude of the relative risk and its statistical precision.

H. Control of Confounding by Cigarette Smoking and Ethnicity

The possible role of cigarette smoking is of concern in any epidemiologic study in which lung cancer or non-malignant respiratory diseases are health outcomes of primary interest. Certainly, this is the case in the present study. Confounding is of paramount concern in epidemiologic research because failure to achieve control for confounding jeopardizes research validity. A confounder can be defined as a factor that is a cause of disease in its own right (i.e., independently of the exposure under study), and is associated with the exposure of interest. There is incontrovertible evidence that cigarette smoking can cause lung cancer and some other respiratory diseases, either in the presence or absence of hazardous occupational exposures. Consequently, the critical issue regarding confounding by smoking is whether smoking is correlated with exposure. In order for cigarette smoking to be a confounder in the present study, the workers' smoking habits would have had to be related to their dust exposures.

There are several approaches for minimizing or eliminating confounding in an epidemiologic study. The most definitive approach is to limit the study to persons without exposure to the suspected confounder. For example, one might choose to study only non-smoking workers and compare their disease risks with non-exposed reference persons who are also non-smokers. This was not a feasible option for this study because we were not certain which workers were and were not smokers. Moreover, eliminating from the study persons with the confounding factor, even when confounder status can be determined validly, makes it impossible to examine synergistic or interactive effects between the exposure and the confounder on disease risk. For example, it would have been of interest to determine whether silica exposure causes greater disease risks among smokers than non-smokers.

When there are valid data on confounding factors, it is possible to adjust the observed associations statistically for unequal distributions of confounders among the various exposure groups. This was done for age, calendar year, duration of follow-up, and ethnicity in the present study. There were some data on smoking available for analysis. These data have been collected by Manville since the early 1960s as part of the company's medical surveillance program. To our knowledge, the other companies did not collect smoking data systematically in the past. We did not consider the smoking data from Manville to be adequately complete or detailed for use in a direct statistical adjustment. We reached this conclusion because the smoking data were available for only 1,113 of the 2,570 workers in the Lompoc cohort, and the data were only sufficiently detailed to classify workers as smokers or non-smokers. Furthermore, in view of the crudeness of the available smoking data, other particularly relevant factors for disease risk, such as duration and amount of smoking, ages started and stopped, and type of cigarettes (filter or non-filter), could not be determined.

Another strategy to minimize confounding is to infer the presence or absence of confounding from the results for a variety of diseases known to be associated with the confounder. Thus, for example, one might observe an excess of lung cancer, and in the absence of data on smoking, infer that the result was or was not an artifact of confounding by smoking, based on the results for other diseases that are known from past evidence to be smoking-related [Steenland et al., 1984].

Another practical approach for evaluating confounding, which like the approach just described, is often necessitated when data on the confounding factor are not available, is to make what are referred to as "indirect" statistical adjustments to the data. The indirect adjustment method requires re-calculation of the results, assuming various correlations between the confounder and the study exposure [Axelson, 1978]. The indirect adjustment approach described by Axelson [1978] requires manipulations of the data based on assumed distributions of a confounder, in this case smoking, by exposure level, and an assumed effect of the confounder on disease risk. An "adjusted" relative risk estimate can be obtained using the following method. First, the amount of the observed relative risk (RR_{obs}) related to the study exposure attributable solely to confounding (RR_{conf}) from smoking can be estimated as [Checkoway and Waldman, 1985]:

$$RR_{conf} = \frac{[(RR_{sm} - 1)(P_{sm/e}) + 1]}{[(RR_{sm} - 1)(P_{sm/ne}) + 1]} \qquad (1)$$

where:

RR_{conf} is the relative risk due solely to confounding by smoking;

RR_{sm} is the relative risk associated with smoking;
$P_{sm/e}$ is the proportion of smokers among the exposed group and,

$P_{sm/ne}$ is the proportion of smokers in the non-exposed (reference) group.

Next, the adjusted relative risk (RR_{adj}) is computed as [Miettinen, 1972]:

$$RR_{adj} = RR_{obs}/RR_{conf}. \qquad (2)$$

An alternative way to use this method, is to compute the prevalence of smoking in the exposed group ($P_{sm/e}$) that would be needed for the adjusted ("true") relative risk to be equal to 1.0, indicating no effect. When there is no effect, $RR_{obs} = RR_{conf}$. This requires assuming specific values of RR_{sm} and $P_{sm/ne}$, and solving for $P_{sm/e}$. We adopted this latter approach in our assessment of the possible confounding influence of smoking.

Ethnicity (Hispanic vs. non-Hispanic) was also considered as a potentially confounding factor. Hispanics are included in the category "white" for the purposes of national vital statistics. Lung cancer rates have been found to be lower among Hispanic than non-Hispanic U.S. white males in numerous studies [USDSHS, 1984; Savitz, 1986; Rosenwaike, 1988; Samet et al., 1988]. One possible explanation for this trend is that Hispanics may smoke less than their non-Hispanic counterparts, (Humble et al., 1985; Marcus and Crane, 1985). There were estimates that as many as 25 percent of Lompoc workers have been of Hispanic ethnic origin, primarily workers born in Mexico. A Cuban-born research associate from the Department of Environmental Health reviewed all of the surnames of the Lompoc cohort and identified the workers of probable Hispanic ethnic origin. Of the 2,570 white males in the Lompoc cohort, 533 were classified as Hispanic. Ethnicity was included as a confounder in the Poisson regression modeling by including a term to denote either Hispanic or non-Hispanic.

Table III.1

Summary of Cohort Identification for the Lompoc Cohort

	Company			
	Manville	Grefco	Both*	Total
•Phase 1 - Identification of as many former employees as possible	12,807	574	39	13,381
•Phase 2 - After elimination of workers employed for < 365 days, based on first & last dates of employment and those last employed prior to 1942	3,333	382	27	3,742
•Phase 3 - After elimination of workers employed for <365 days, based on full work history information	2,633	341	29	3,003
Main Study Cohort - White (including Hispanic) males without known asbestos exposure, excluding those with missing work histories or birth date	2,243	299	28	2,570

* Workers employed at both Manville and Grefco; the numbers in this column fluctuate due to new information from work history records.

Table III.2
Representative Industrial Hygiene Sampling Results:
Manville, Lompoc Plant 1978-1987

Exposure level/ Job title	Total dust (mg/M^3)	Respirable dust (mg/M^3)
Low		
Boiler Operator	0.614	0.116
Lab Technician	0.432	0.113
Erection & Repair Shop	0.370	0.167
Intermediate		
Auto Pack Station	1.071	0.131
Acid Wash (AWFA)	2.011	0.201
Quarries & Mines	0.913	0.204
Tite Pac Operator	1.948	0.180
High		
Dust Leak Patcher	5.904	0.613
Mill Janitor	3.637	0.274
Packer	2.466	0.341
Re-feeder	3.394	0.433

Table III.3
Weighted Dust Exposure Factors Accounting for Changes in Dust Concentrations and Use of Respirators

	Time Period				
Exposure Level	Before 1944	1944-53	1954-63	1964-73	1974-87
Non-exposed	0.0	0.0	0.0	0.0	0.0
Low	12.0	6.0	2.0	1.5	1.0
Intermediate	36.0	18.0	5.2	3.0	1.4
High	72.0	36.0	10.0	5.25	2.0

Table III.4
Numbers of Workers by Type of DE Exposure:
2,570 White Males, Lompoc Cohort

Type of DE	No.	(%)
Non-exposed	121	(4.7)
Natural only	129	(5.0)
Calcined only	1,273	(49.5)
Mixed Natural and Calcined	1,047	(40.8)
Total:	2,570	

CHAPTER IV

RESULTS

This chapter presents the results of the mortality analyses, including comparisons against the national and regional populations, and mortality rate comparisons among subgroups of DE cohort members.

The data are organized in the following manner. The principal analyses were conducted among 2,570 white males employed for at least 12 months at the Lompoc facilities. Hereafter, these workers are referred to as the "Lompoc cohort." As described in Chapter III, other groups of DE workers (104 white males probably exposed to asbestos; black males, white females, and workers from non-Lompoc DE plants) were excluded from the Lompoc cohort, and their data were analyzed separately. Descriptive statistics regarding vital status tracing and cause of death ascertainment, and distributions of duration of employment and other pertinent variables are presented first. Next, data from the cause-specific mortality rate comparisons against the national and regional populations are presented. This section is then followed by detailed analyses of the mortality patterns for the two disease categories of greatest interest: lung cancer and non-malignant respiratory diseases (NMRD). Comparisons against U.S. mortality rates are shown according to time-related variables (e.g., time since first employment, duration of employment). The main analyses that address issues of dose-dependency follow. These include within-cohort (i.e., internal) comparisons among subcohorts classified according to the following exposure indices:

1) total duration of employment in DE industry jobs

2) duration of employment in "dust-exposed" DE jobs

3) duration of employment in dust-exposed jobs weighted according to exposure intensity, with weights defined with respect to temporal changes in dust exposure levels, use of respiratory protection, and job-specific differences in exposure level

4) estimated cumulative exposure to crystalline silica, based on job- and time-specific exposure intensity weightings, proportions of the types of DE materials

(natural, calcined, flux-calcined) produced and handled in the various job categories over time, and the percentages of crystalline silica in the product mixes.

Data from these internal comparison analyses are shown in reference to assumed disease latency intervals of 0, 5, and 15 years. Separate sets of findings are presented for lung cancer and NMRD to facilitate review of the data. Results are presented sequentially for the least specific exposure metric (total duration of employment) to the most specific dose indicator (estimated cumulative exposure to crystalline silica).

The next two sections contain data pertinent to the issue of potential confounding from cigarette smoking and ethnicity (Hispanic vs. non-Hispanic), and the possible extent of bias introduced by incomplete vital status ascertainment. Throughout, findings are presented separately for lung cancer and NMRD among the Lompoc cohort.

The remaining sections of this chapter present mortality data for the following groups of DE workers:

1) Lompoc white males potentially exposed to asbestos

2) Black males employed at the Lompoc facilities

3) White female workers employed at the Lompoc plants

4) Basalt, Nevada plant workers (all white males)

5) Quincy, Washington plant workers (all white males).

Because of the small sizes of these latter five groups, and hence the small numbers of deaths, the analyses were limited to comparisons against national mortality rates for selected disease categories: all causes combined, all cancers, lung cancer, and NMRD.

A. Lompoc Cohort - Descriptive Statistics

As shown in Table IV.1, vital status tracing was completed successfully for 91 percent of the cohort, and death certificates were obtained for 591 of 628 (94%) of identified deaths. Approximately 24 percent of workers died during the follow-up interval, 1942-87. The percentage of vital status tracing is somewhat lower than the nominally desired target of 95 percent or higher. The percentage of death certificates retrieved can be considered as acceptable, although it should be appreciated that, in the comparisons against the national and regional external populations, the SMRs will be slightly underestimated for some causes because some of the deaths in the cohort assigned to an unknown cause are in fact attributable to specific diseases. The extent of underestimation of cause-specific SMRs is not likely to be large, however. The sources used to determine alive status are listed in Table IV.2. Personnel records indicating actively employed status (26%), motor vehicles bureau data (42%), and credit bureaus (27%) were the major sources used to infer living status.

The distributions of age at first employment, year of first employment, and duration of employment are given in Tables IV. 3, 4, and 5, respectively. As is typical of many manufacturing and mining industries, most workers were first hired before age 30; the median age of first hire was 24 yr. The peak decades of first employment were the 1940s and 1950s (median year 1953), accounting for over half of all first hires. The majority of workers was employed for less than 5 yr; the median employment duration for the study cohort was approximately 4 yr. However, nearly 30 percent of workers had relatively long durations of employment (≥10 yr), which is an important consideration in studies of diseases postulated to be linked with long-term exposures. It is noteworthy in this regard that roughly 60 percent of the cohort was followed for at least 20 yr (Table IV.6). Ten years is often considered to be a minimum follow-up duration to yield meaningful data in studies of cancer and other chronic diseases. Twenty-nine (29) percent (749 of 2,570) of the cohort was employed for at least 5 yr and followed for at least 20 yr (Table IV.7). The person-years of observation distribution, cross-classified according to duration of follow-up and duration of employment, is presented in Table IV.8. The preponderance of person-years in the shortest employment duration stratum (< 5 yr), in contrast to the distribution of persons shown in Table IV.5, occurred because each cohort member contributed person-time into each category (beginning with the lowest) as time passed.

B. Lompoc Cohort - General Patterns of Cause-Specific Mortality

SMRs, relative to prevailing rates for U.S. white males, are given for major cause of death categories in Table IV.9. Mortality from all causes combined was slightly elevated (SMR=1.12). Among non-cancer diseases, the largest excess was seen for the non-malignant respiratory diseases (77 Obs vs. 34.0 Exp), especially in the category of "pneumoconioses and other respiratory diseases" (41 Obs vs. 12.5 Exp). Among the 41 deaths in this grouping, the death certificates listed 5 deaths with "Silicosis," 5 with "Diatomaceous Earth Pneumoconiosis," and 7 with "Pneumoconiosis" as the underlying cause of death. For purposes of the remaining analyses, the NMRD category was re-defined as all non-malignant respiratory diseases except infectious diseases and pneumonia. The SMR for NMRD was 2.59, based on 56 observed and 21.7 expected deaths.

All causes SMRs of 0.7-0.9 are typically seen for industrial cohorts when comparisons are made with national populations because of the "Healthy Worker Effect." Worker populations who are sufficiently healthy to gain and maintain employment usually have lower overall mortality risks relative to national populations which include persons chronically ill or otherwise unfit for employment [Fox and Collier, 1976]. Relative mortality rate deficits for cardiovascular diseases and other non-malignant diseases are the most common manifestations of the Healthy Worker Effect [McMichael et al., 1976]. With the exception of non-malignant respiratory diseases, diabetes, and non-malignant genitourinary diseases, this cohort has experienced the Healthy Worker Effect.

The excesses of renal diseases, although based on small numbers, may be noteworthy in view of some evidence suggesting a nephrotoxic effect of crystalline silica [Ng et al., 1992]. However, risks for non-malignant renal diseases are difficult to assess in a mortality study because a substantial proportion of renal disease is subacute or non-fatal.

Site-specific cancer SMRs are given in Table IV.10. Of greatest interest is the excess of lung cancer (SMR=1.43; 59 Obs vs. 41.4 Exp). The mortality patterns for cancers of other sites are unremarkable. The excess of cancers of the brain and central nervous system (SMR=1.53; 6 Obs vs. 3.92 Exp) was based on small numbers and was not an anticipated finding.

C. Lompoc Cohort - Lung Cancer

Lung cancer SMRs were computed relative to rates in several alternative reference populations: white males in the U.S., Southern California, and the four local counties (Table IV.11). The mortality excesses in the cohort were slightly larger compared to the latter two reference populations because lung cancer mortality rates were lower in these areas than in the entire U.S. during the years of follow-up. Rates in the U.S. white male population were used for comparison in the remaining analyses involving external reference rates.

The patterns of lung cancer SMRs, by year of death, year of hire, time since first employment, and age at death are given in Table IV.12. The largest relative excesses (SMRs) were found for the 1950-59 decade of death, and among persons hired before 1930. Age at death was not consistently related to excess mortality. The relatively high SMR for <10 yr since first employment (SMR=2.10) is based on only 3 deaths. However, the SMR of 1.50 for workers ≥30 yr since first hire is based on a substantially larger number of deaths (33), and is consistent with an exposure effect requiring a long induction time.

There is an irregular gradient of excess lung cancer SMRs with respect to total duration of employment in the DE industry; however, a more consistent pattern of increasing risk was detected for duration of employment in "dust-exposed" DE jobs (Table IV.13).

The set of analyses to be reported next was conducted to estimate dose-response trends more thoroughly, and involved mortality rate contrasts among subgroups of the Lompoc cohort (i.e., internal comparisons). The data presented are expressed in terms of relative risks (RR) in reference to the lowest exposure category (e.g., shortest employment duration, lowest cumulative exposure to dust).

The person-years distribution by employment duration and latency interval is given in Table IV.14. Lung cancer relative risks (RRs) increased with increasing employment duration longer than 5 yr, but the trend is irregular (Table IV.15). However, when 5 and 15 yr latency intervals were taken into account the patterns of risk with employment duration suggest stronger associations. Allowing for a 15-yr latency, the relative risks increase monotonically from 1.00 (<5 yr, reference) to 2.24 for workers employed for 20 yr and longer.

Table IV.16 displays the person-year distributions by duration of employment in dust-exposed jobs and latency. The trends of risk are more linear and pronounced when employment duration was restricted to dust-exposed jobs (Table IV. 17). The strongest effect can be seen in Table IV.17 for ≥20 yr employment in dust-exposed jobs, assuming a 15-yr latency (RR=2.88).

Person-year distributions and trends of lung cancer mortality in relation to employment duration in dust-exposed jobs, weighted by exposure intensity, are displayed in Tables IV.18 and 19, respectively. As described previously in Chapter III, the exposure weights included scaling factors for job-specific differences in exposure intensity, temporal changes in exposure, and the use of respiratory protection. The gradients of lung cancer risk are not uniformly increasing, yet demonstrate reasonably strong effects among workers in the highest exposure strata. In particular, an RR estimate of 2.46 was computed for the highest cumulative exposure category under a 15-yr latency assumption. These gradients were somewhat less pronounced than the trends detected for unweighted duration of exposure to dust (Table IV.17).

The final analyses of the lung cancer mortality data were conducted in reference to estimated cumulative exposures to crystalline silica, which were estimated using scaling factors for job- and time-specific differences in exposure intensity, as well as the distributions of the various DE product types and the corresponding percentages of crystalline silica in the respirable fractions of the dust. The person-year distributions by exposure and latency are given in Table IV.20, and the RR trends are presented in Table IV.21. Increasing risk gradients were observed throughout, especially under a 15-yr latency assumption in which the RR trend increased monotonically from 1.00 to 2.74. As a check on the sensitivity of the findings to the choice of exposure intensity weights, we conducted analyses in which the weights were varied as 1,2, 4; 1,3,6; or 1,4, 8. The lung cancer trends with crystalline silica exposure, assuming a 15-year latency, did not vary markedly when the weights were altered (Table IV.22), which suggests that the observed gradient is unlikely to be an artifact of the exposure intensity weights chosen. Weights of 1,3, 6 were used in the remaining analyses, except where indicated.

D. Lompoc Cohort - Non-Malignant Respiratory Diseases

In these analyses, NMRD is defined as chronic non-cancer diseases of the respiratory system, including chronic bronchitis, emphysema, asthma, and the pneumoconioses. Two deaths coded to infectious diseases were eliminated from this category, as were 19 deaths attributed to pneumonia as the underlying cause of death. Ideally, we would have conducted analyses restricted to silicosis; however, uncertainties of death certificate classification of silicosis precluded this more specific evaluation.

The data presented in this section of Chapter IV follow a similar pattern as the reporting of the lung cancer findings. The main difference is that regional (Southern California and local county) mortality rates for NMRD are only available for the years 1960 and later; thus, we limited the SMR contrasts to rates among the cohort and U.S. white males.

SMRs by year of death, year of hire, time since first employment, and age at death are displayed in Table IV.23. The patterns with respect to these time-related factors are very irregular, and are thus difficult to interpret. Table 24 shows the frequencies of pneumoconiosis and other types of NMRD according to the same time-related variables. Only 17 of the 56 deaths in the overall NMRD category were coded as 'Pneumoconiosis, 'which included 'silicosis,' 'diatomaceous earth pneumoconiosis,' and pneumoconiosis not otherwise specified, as underlying cause of death on death certificates. There were no deaths attributed to asbestosis in the cohort. It is noteworthy that no deaths attributed to pneumoconiosis occurred among workers hired since 1950. This pattern may indicate a reduction of silicosis risk in the cohort; however, any interpretation should be tempered by the realization that death certificate information is generally a poor source of data on this disease. Review of chest x-ray and clinical information would be needed to reach firm conclusions about the temporal pattern of silicosis risks.

Excess NMRD mortality, based on SMR gradients, was not consistently associated with either total duration of employment in DE jobs or in duration of employment in dust-exposed jobs (Table IV.25). The remaining analyses evaluated mortality rate trends using internal reference subcohorts.

Relative risks for NMRD are shown by total duration of DE employment in Table IV.26. (The corresponding person-years distributions, by latency interval, for these results and for the remaining analyses of NMRD are identical to those shown in the preceding section on the lung cancer data; see Tables IV.14, 16, 18, 20.) The trends of NMRD mortality with employment duration were strongest under a 15-yr latency assumption, but were not monotonically increasing. Duration of employment in dust-exposed jobs demonstrated similar associations with NMRD as were seen for total employment duration; the most consistently increasing gradient for dust exposure duration was found when a 15-yr latency was assumed (Table IV.27).

As can be seen from the data in Table IV.28, employment duration in dust-exposed jobs, weighted by exposure intensity, bore fairly strong associations with NMRD. As with most of the preceding results, the trend was most pronounced when a 15-yr latency was assumed (RR=2.63 in the highest exposure category).

The final analysis of the NMRD examined relative risks with respect to estimated cumulative exposures to crystalline silica. As displayed in Table IV.29, the trends were consistently strong. Assuming various latency intervals did not materially alter the trends with cumulative crystalline silica exposure, as the RRs increased to approximately 2.7 to 2.9 in the highest exposure stratum. The NMRD mortality risk gradients with crystalline silica, lagged 15 years, persisted when the exposure weights were varied; the strongest association was observed when weights of 1,3,6 were applied (Table IV.30).

E. Potential Confounding by Cigarette Smoking and Ethnicity

It is useful to examine the observed risks associated with smoking status, based on the limited data available on smoking. Tables IV.31 and IV.32, respectively, show SMRs for lung cancer and NMRD according to assumed smoking status, classified as "ever" or "never" smoked. The ever smokers include workers who were recorded as either "current" or "former" cigarette smokers at the times when the smoking history information was obtained. Included among the 345 "non-smokers" are 47 workers for whom the data indicated that they were pipe or cigar, but not cigarette, smokers. Thus, smoking status refers to cigarette smoking only. It appears that smokers and persons with unknown smoking status (which undoubtedly include some smokers) experienced substantially higher lung cancer and NMRD risks than workers classified as non-smokers. It should be recognized that the comparisons between subgroups of the cohort, classified by smoking status, and the national population, which includes both smokers and non-smokers, are not strictly valid because each comparison is confounded by smoking (i.e., the smokers in the U.S. population increase overall rates and thus exaggerate the mortality deficits in non-smokers among the cohort). Nonetheless, these results indicate the anticipated effects of smoking habits, notwithstanding the incompleteness of the smoking information.

In a similar manner, we examined the effects of Hispanic ethnicity on lung cancer and NMRD risks. SMRs for lung cancer and NMRD were both lower among the 533 Hispanics than among the 2,037 non-Hispanic white males in the cohort (Table IV.33). The lung cancer differential is, in fact, quite pronounced; SMR=0.33 for Hispanics vs.

SMR=1.74 for non-Hispanics. The possibility exists that proportionately fewer Hispanics smoked cigarettes than non-Hispanics, or that the amounts smoked were less among Hispanic than non-Hispanic smokers.

In considering whether there is evidence for confounding by smoking, one can review the cohort's mortality patterns for the known smoking-related diseases other than lung cancer and NMRD [Steenland et al., 1984]. These include cancers of the oral cavity, esophagus, larynx, pancreas, kidney, and bladder. As can be seen from the data in Table IV.10, there were either no or very small excesses for each of these diseases. It could be argued that an excess of emphysema, which we included in the NMRD category, might be an indicator of smoking habits. This is a possibility, and the nearly two-fold excess for emphysema (see Table IV.9) supports such an argument. Although we would have preferred to separate the individual types of NMRD and perform more specific analyses, we were relying on death certificate diagnoses which are of uncertain quality for non-malignant respiratory diseases. There is the possibility that some of the deaths assigned to emphysema were, in fact, related to dust exposure (e.g., silicosis).

Our second approach for examining the possibility of confounding involved assessing the likelihood that either smoking or ethnicity was related to exposure. We examined the available smoking data to determine whether there were correlations with exposure, which would indicate the possibility of confounding. In particular, we focused on what we regard as the most meaningful exposure index, estimated cumulative crystalline silica exposure, lagged 15 years to allow for a 15-yr latency interval, and its relation to lung cancer. The smoking data were not entered directly into the Poisson regression analyses because the data were judged to be too incomplete, and because there were too few lung cancer deaths among non-smokers to yield statistically reliable relative risk estimates. Instead, we examined the distributions of smoking status by exposure category, and performed separate analyses among the identified smokers.

Table IV.34 gives the distribution of smoking status, determined from the available data, by cumulative crystalline exposure category, and by decade of birth for the Lompoc cohort. The data were stratified by birth year because smoking prevalence has varied greatly by birth cohort in the U.S. [Harris, 1983]. As shown in Table IV.35, the proportion of smokers among persons with "known" smoking status was somewhat smaller in the lowest category (65%) than the others, but the distribution is fairly uniform at the higher exposure levels (78-79%). When comparisons of smoking prevalence were limited to workers born between 1890 and 1939, the birth cohorts for which smoking data were available for at least some workers in all four exposure categories, only very minute differences were detected; smoking prevalence (not adjusted for birth cohort) ranged from 77.5 to 79.3 percent across exposure categories. The prevalences of smoking in Table IV.36 are shown with and without adjustment for decade of birth. Adjusted prevalences for the four exposure categories were standardized first according to the birth year distribution of all 1,765 white males born between 1890 and 1939, and second according to the birth year distribution of the subset of these workers (544) with known smoking information. The patterns of smoking prevalence did not change materially after adjustment.

Table IV.37 gives lung cancer relative risk estimates for crystalline silica exposures, assuming a 15-year latency, for the 1,765 workers born between 1890 and 1939. This analysis was conducted under the assumption that smoking prevalence did not differ by exposure level among workers born during that time period. The relative risk trend is increasing with exposure, and is very similar in magnitude to the corresponding trend observed for the entire cohort of 2, 570 white males (see Table IV.21).

Another evaluation of the potential for confounding by smoking habits involved performing a separate exposure-response analysis of lung cancer among the 768 workers who were classified as smokers. (There were too few lung cancer deaths among non-smokers for a meaningful analysis of this type.) In this analysis, we assumed that the identified smokers were smokers throughout their working careers. This unverifiable assumption was necessitated because data indicating change in smoking status were not available; in fact, most of the dates in the medical record data indicating when smoking status was determined were during the 1980s. Thus, follow-up for the smokers began at the later of 1 January 1942 or the date when 12 months cumulative service was achieved, as in the previous analyses for the entire cohort. The small number of lung cancer deaths among the smokers (18) did not permit a full Poisson regression analysis of relative risk. Instead, we computed SMRs relative to rates among U.S. white males. The pattern of SMRs by crystalline silica exposure level, allowing for a 15-year latency, is consistent with a dose-response relationship, despite the small numbers of observed deaths (Table IV.38).

To assess further the possibility of confounding by smoking, we followed Axelson's [1978] method of indirect adjustment of observed relative risks, described previously in Chapter III. Using expressions (1) and (2) to estimate the relative risk due to confounding, it is possible to determine the proportion of smokers in each exposure category required to reduce the observed relative risk to the null value of 1.0. This involves assuming particular values for the prevalence of smoking among the reference category ($P_{sm/ne}$) and the relative risk associated with smoking (RR_{sm}), and solving expression (1) for the prevalence of smoking in each exposure group ($P_{sm/e}$). Thus, from expression (2), it can be seen that the "true," or adjusted, RR for exposure would be equal to 1.0 when the RR due to confounding (RR_{conf}) is equal to the observed RR (RR_{obs}). Substituting RR_{obs} for RR_{conf} in expression (1) will permit estimation of Psm/e required for there to have been no association between exposure and disease risk.

Table IV.39 shows ranges of values of $P_{sm/e}$ at each level of cumulative crystalline silica exposure, lagged by 15 years, necessary to reduce the observed exposure-response trend for lung cancer to a completely flat curve indicating no association (i.e., all RR values equal 1.0). In these calculations, a relative risk for smoking of 10 was assumed, based on a compilation of data on current smoking and lung cancer reported in the 1989 U.S. Surgeon General's Report on the health consequences of smoking [U.S. DHHS, 1989]; reported relative risks among men in Western countries varied from approximately 7 to 16. Lower relative risks, roughly 2-8 have been found for persons who quit smoking [U.S. DHHS, 1990]; consequently, 10 seems to be a reasonable estimate of relative risk for "ever" smokers. Separate calculations were made for values of smoking prevalence in the lowest exposure group ranging from 0.3 to 0.5. Values larger than 1.0 are impossible, as the upper bound on smoking prevalence is 100 percent. These hypothetical calculations reveal that the observed risk gradient for crystalline silica and lung cancer mortality would only be an artifact of smoking habits if smoking had been directly associated with cumulative exposure. Moreover, it would be impossible for smoking to account completely for the excess in the highest exposure category, given an assumed relative risk of 10 for ever smokers.

Potential confounding by Hispanic ethnicity was addressed in the internal analyses by statistical adjustment in the Poisson regression modeling. The distribution of Hispanics did not differ substantially according to crystalline silica exposure lagged by 15 years (Table IV.40). Moreover, the exposure-response trend for lung cancer was not materially different from that noted for the entire cohort when the analysis was limited to 2,037 non-Hispanic white males (Table IV.41).

The data on smoking status and Hispanic ethnicity by exposure level do not demonstrate sufficiently strong correlations between these factors and crystalline silica exposure to have caused severely confounded results. Moreover, the results for lung cancer with respect to crystalline silica exposure among smokers and among non-Hispanic white males are consistent with the trend seen for the entire cohort, which suggests that confounding by these factors was unlikely to account for the observed association.

F. The Influence of Incomplete Vital Status Ascertainment

Bias in the results may have occurred because of incomplete follow-up. The attained follow-up rate for the study cohort (91%) is less than the desired target of 95 percent or greater. It is conceivable that some of the cause-specific SMRs, relative to the U.S. population, may be somewhat inflated due to cessation of follow-up at the dates of last observation for workers with unknown vital status. In other words, some of the workers with unknown vital status may have been alive at the end date of the study (1 Jan. 1988), and thus the expected numbers that were computed would have been underestimated. It is possible to estimate the maximum amount of overestimation of the SMRs attributable to incomplete vital status determination by re-calculating SMRs under the assumption that all of the unknowns survived until the end of the follow-up period. As shown in Table IV.42, the entire Lompoc cohort's SMRs for lung cancer and NMRD are diminished somewhat when this rather extreme assumption is made, but still remain elevated. Nonetheless, the patterns of association with duration of employment in dust-exposed jobs, indicated by SMR trends, for lung cancer (Table IV.43) and NMRD (Table IV.44) are not materially changed. It should also be recognized that failure to collect death certificates for some of the deaths will have a counter-balancing effect (i.e., lowering) on some cause-specific SMRs because the deaths of unknown cause include some deaths that were, in fact, attributable to specific diseases. The net effect of bias caused by incomplete vital status and cause of death ascertainment was probably small in the SMR comparisons with national rates and in the subcohort analyses by exposure category.

G. Mortality Results: Other Workers

This section describes the mortality patterns for the following groups of workers not included in the main Lompoc cohort: 104 white male Lompoc plant workers with potential exposures to asbestos; 37 black male Lompoc plant workers; 242 white female

Lompoc plant workers; 158 white male workers from the Basalt, Nevada plant; and 121 workers from the Quincy, Washington plant. All workers included in these groups worked for at least 12 months cumulative service.

Because of small numbers in these groups, the analyses presented were limited to SMR contrasts with the U.S. population for the following disease categories: all causes combined; all cancers; lung cancer, and NMRD. In view of the sparseness of the data, any inferences drawn from these results are necessarily limited.

1. <u>White Males Exposed to Asbestos</u>

The vital status tracing and cause of death determination results are summarized in Table IV.45. Follow-up was completed for 98 of the 104 (94.3%) workers. This group experienced excesses of lung cancer (SMR=3.54; 4 Obs vs. 1.13 Exp) and NMRD (SMR=1.97; 1 Obs vs. 0.51 Exp), as shown in Table IV.46.

2. <u>Black Male Lompoc Workers</u>

Only one death occurred among the 37 workers (Table IV.47), and this was due to lung cancer. The lung cancer SMR of 5.23 is thus based on 1 Obs and 0.19 Exp (Table IV.48).

3. <u>White Female Lompoc Workers</u>

This group consisted of 242 workers, of whom 31 (12.8%) died during the follow-up interval (Table IV.49). As shown in Table IV.50, there were apparent elevations of risk for lung cancer (SMR=2.76; 3 Obs vs. 1.09 Exp) and NMRD (SMR=7.77; 5 Obs vs. 0.64 Exp).

4. <u>Basalt Plant Workers</u>

All of the 158 workers forming the cohort for this plant were white males. During the follow-up period 32 deaths occurred. We obtained death certificates for 26 (81%) of these deaths (Table IV.51). Compared to U.S. white males the SMRs for lung cancer and NMRD were, (Table IV.52), respectively, 1.69 (4 Obs vs. 2.37 Exp) and 0 (0 Obs vs. 1.12 Exp).

5. Quincy, Washington Plant Workers

This group included 121 white males, and vital status was determined for all of these workers (Table IV.53). Only 6 deaths occurred during the study period. None of these deaths was due to lung cancer or NMRD (Table IV.54).

Table IV.1

Vital Status and Cause of Death Determination for 2,570 White Males:

Lompoc Cohort

Vital status	No.	(%)
Alive as of 1 Jan. 1988	1,719	(66.9)
Dead — Total	628	(24.4)
- with certificate	591	(94.1)†
- without certificate	37	(5.9)†
Unknown	223	(8.7)
Total	2,570	

†Percent of total identified deaths

Table IV.2

Sources for Determination of Vital Status as Alive as of 1 Jan 1988

For 1,719 of 2,570 White Males in the Lompoc Cohort

Source/reason	No. of workers	(%)
Actively employed after 1 Jan. 1988	438	(25.5)
Died after 1 Jan. 1988	60	(3.5)
Motor vehicles bureaus	715	(41.6)
National Death Index (no match)	36	(2.3)
Credit bureaus	467	(27.2)
Total	1,719	(100)

Table IV.3

Age at First Employment for 2,570 White Males:

Lompoc Cohort

Age (yr)	No.	(%)
<20	544	(21.2)
20-29	1339	(52.1)
30-39	471	(18.3)
40-49	178	(6.9)
50-64	38	(1.5)

Mean (SD): 26.6 (8.0)

Median: 24.2

Range: 15 - 60

Table IV.4

Year of First Employment for 2,570 White Males:

Lompoc Cohort

Year	No.	(%)
Before 1930	67	(2.6)
1930-39	140	(5.4)
1940-49	757	(29.5)
1950-59	630	(24.5)
1960-69	490	(19.1)
1970-79	335	(13.0)
1980-86	151	(5.9)

Mean (SD): 1956 (14.2)

Median: 1953

Range: 1908 - 1986

Table IV.5
Duration of Employment for 2,570 White Males:
Lompoc Cohort

Duration (yr)	No.	(%)
1-4	1456	(56.7)
5-9	379	(14.7)
10-19	327	(12.7)
20-29	265	(10.3)
≥30	143	(5.6)

Mean (SD): 8.75 (9.91)
Median: 3.95
Range: 1 - 46.5

Table IV.6

Duration of Follow-up for 2,570 White Males:

Lompoc Cohort

Duration (yr)	No.	(%)
<5	323	(12.6)
5-9	232	(9.0)
10-19	451	(17.5)
20-29	618	(24.0)
≥30	946	(36.8)

Mean (SD): 23.8 (13.8)

Median: 24.5

Range: <1 - 64.5

Table IV.7
Duration of Employment by Duration of Follow-up for 2,570 White Males:
Lompoc Cohort

Duration of employment (yr)	Duration of follow-up (yr)				
	<5	5-9	10-19	20-29	≥30
<5	312 (12.1)†	109 (4.2)	220 (8.6)	284 (11.1)	531 (20.7)
5-9	11 (0.4)	107 (4.2)	57 (2.2)	89 (3.5)	115 (4.5)
10-19	--	16 (0.6)	169 (6.6)	69 (2.7)	73 (2.8)
20-29	--	--	5 (0.2)	176 (6.8)	84 (3.3)
≥30	--	--	--	--	143 (5.6)

†Percent of total (2,570)

Table IV.8

Person-Years at Risk by Duration of Employment and Duration of Follow-up:
2,570 White Males, Lompoc Cohort

Duration of Follow-up (yr)	Duration of employment (yr)				
	<5	5-9	10-19	≥20	Total
< 10	15,995	5,192	1,046	202	22,435
10 - 19	9,404	2,479	5,349	667	17,899
≥ 20	10,646	2,388	1,589	4,345	18,968
Total	36,045	10,059	7,984	5,214	59,302

Table IV.9

Observed and Expected Deaths and Standardized Mortality Ratios for Major Cause of Death Categories: 2,570 White Males, Lompoc Cohort

Cause of death	Obs	Exp†	SMR	(95% CI)‡
All causes	628	563	1.12	(1.03 - 1.21)
All cancers	132	121	1.09	(0.91 - 1.29)
Diabetes mellitus	8	7.89	1.01	(0.44 - 2.00)
Ischemic heart disease	159	187	0.85	(0.72 - 0.99)
Cerebrovascular disease	30	30.9	0.97	(0.66 - 1.39)
Digestive disease	21	28.5	0.74	(0.46 - 1.13)
Genito-urinary diseases	10	7.06	1.42	(0.68 - 2.61)
-Glomeruluonephritis, Renal Failure	2	0.63	3.17	(0.38 - 11.5)
-Chronic nephritis	4	3.31	1.21	(0.33 - 3.10)
Non-malignant respiratory disease	77	34.0	2.27	(1.79 - 2.83)
-Acute upper resp. infections	1	0.23	4.35	(0.11 - 24.3)
-Influenza	1	0.60	1.66	(0.04 - 9.23)
-Pneumonia	19	11.5	1.65	(0.99 - 2.58)
-Chronic bronchitis	1	1.45	0.69	(0.02 - 3.85)
-Emphysema	12	6.69	1.80	(0.93 - 3.14)
-Asthma	2	1.02	1.96	(0.24 - 7.08)
-Pneumoconioses and other respiratory diseases	41	12.5	3.29	(2.36 - 4.46)
-NMRD except pneumonia and infectious diseases	56	21.6	2.59	(1.96 - 3.36)
Nervous system diseases	5	5.81	0.86	(0.28 - 2.01)
Accidents	51	42.4	1.20	(0.90 - 1.58)

†Based on rates for U.S. white males 1942-87

‡ 95 percent confidence interval for SMR

Table IV.10

Observed and Expected Deaths and Standardized Mortality Ratios for Site-Specific Cancers: 2,570 White Males, Lompoc Cohort

Cause of death	Obs	Exp†	SMR	(95% CI)‡
All sites combined	132	121	1.09	(0.91 - 1.29)
Buccal cavity and pharynx	3	3.62	0.83	(0.17 - 2.42)
Esophagus	0	2.89	0	(0 - 1.28)
Stomach	5	5.39	0.93	(0.30 - 2.16)
Colon	13	10.9	1.19	(0.64 - 2.04)
Rectum	1	3.18	0.32	(0 - 1.76)
Liver	3	2.79	1.08	(0.62 - 8.76)
Pancreas	7	6.30	1.11	(0.45 - 2.29)
Larynx	2	1.74	1.15	(0.14 - 4.15)
Lung	59	41.4	1.43	(1.09 - 1.84)
Prostate	6	7.30	0.82	(0.30 - 1.79)
Kidney	2	3.07	0.65	(0.08 - 2.35)
Bladder	2	3.14	0.64	(0.08 - 2.30)
Skin	2	2.54	0.79	(0.10 - 2.85)
Brain and CNS	6	3.93	1.53	(0.56 - 3.33)
Lymphosarcoma and reticulosarcoma	0	2.17	0	(0 - 1.70)
Hodgkin's disease	1	1.33	0.75	(0.02 - 4.19)
Leukemia	1	4.77	0.21	(0.01 - 1.17)
Other hematologic malignancies	2	3.39	0.59	(0.07 - 2.13)

† Based on rates for U.S. white males, 1942 -87

‡ 95 percent confidence interval for SMR

Table IV.11

Observed and Expected Deaths and Standardized Mortality Ratios for Lung Cancer Based on Various External Reference Rates: 2,570 White Males, Lompoc Cohort, 1950-87

Reference population	Obs	Exp	SMR	(95% CI)‡
All U.S.	59	41.4	1.43	(1.09 - 1.84)
Southern California*	59	37.8	1.56	(1.19 - 2.01)
Four local counties**	59	37.1	1.59	(1.21 - 2.05)

† 95 percent confidence interval for SMR

* Includes: Imperial, Kern, Los Angeles, Orange, Riverside, Santa Barbara, San Bernadino, San Diego, San Luis Obispo, and Ventura Counties.

** Includes: Kern, Santa Barbara, San Luis Obispo, and Ventura Counties

Table IV.12

Observed and Expected Deaths and Standardized Mortality Ratios for Lung Cancer by Year of Death, Year of Hire, Time Since First Employment, and Age at Death: 2570 White Males, Lompoc Cohort

Variable	Person-yrs	Obs	Exp†	SMR	(95% CI)
Year of death					
1942-49	3,901	0	0.34	0	(0 - 10.9)
1950-59	10,227	6	2.02	2.96	(1.09 - 6.45)
1960-69	14,639	7	6.70	1.04	(0.42 - 2.15)
1970-79	16,677	24	14.6	1.65	(1.05 - 2.45)
1980-87	13,905	22	17.7	1.24	(0.78 - 1.88)
Year of hire					
Before 1930	2,048	8	3.06	2.63	(1.12 - 5.15)
1930-39	4,246	8	4.65	1.72	(0.74 - 3.39)
1940-49	21,946	27	20.5	1.32	(0.87 - 1.92)
1950-59	16,837	14	10.5	1.33	(0.72 - 2.23)
1960-69	10,166	2	2.45	0.82	(0.10 - 2.96)
1970-86	4,106	0	0.23	0	(0 - 16.4)
Time since first employment(yr)					
<10	18,303	3	1.43	2.10	(0.43 - 6.14)
10 - 19	18,184	6	5.54	1.08	(0.40 - 2.36)
20 - 29	13,371	17	12.2	1.39	(0.81 - 2.23)
≥ 30	9,492	33	22.2	1.50	(1.02 - 2.09)
Age at death					
< 40	25,028	0	0.61	0	(0 - 6.09)
40 - 49	15,052	5	4.10	1.22	(0.40 - 2.85)
50 - 59	11,513	22	12.8	1.72	(1.08 - 2.60)
60 - 69	5,849	19	15.7	1.21	(0.73 - 1.89)
≥ 70	1,907	13	8.21	1.58	(0.84 - 2.71)

† Based on rates for U.S. White Males, 1942 - 87

‡ 95 percent confidence interval for SMR

Table IV.13

Observed and Expected Deaths and Standardized Mortality Ratios for Lung Cancer by Total Duration of Employment and Duration of Employment in Dust-Exposed Jobs: 2,570 White Males, Lompoc Cohort

Variable	Person-yrs	Obs	Exp†	SMR	(95% CI)‡
Total duration of employment (yr)					
1 - 4	36,068	20	21.3	0.94	(0.57 - 1.45)
5 - 9	10,065	12	5.58	2.15	(1.11 - 3.76)
10 - 19	7,978	9	5.91	1.52	(0.70 - 2.89)
≥ 20	5,238	18	8.53	2.11	(1.25 - 3.34)
Duration of employment in dust-exposed jobs (yr)					
< 5	38,349	24	23.7	1.01	(0.65 - 1.51)
5 - 9	9,503	10	5.65	1.77	(0.85 - 3.25)
10 - 19	7,556	11	5.75	1.92	(0.96 - 3.43)
≥ 20	3,941	14	6.15	2.28	(1.23 - 3.76)

† Based on rates for U.S. white males 1942 - 87

‡ 95 percent confidence interval for SMR

Table IV.14

Person-years of Observation and Numbers of Workers, by Total Employment Duration and Latency Interval: 2,570 White Males, Lompoc Cohort *

Duration of Employment (yr)	Latency interval (yr) 0		5		15	
1 - 4 (reference)	36,045†	(1,456)‡	40,953	(1,570)	49,469	(1,809)
5 – 9	10,059	(379)	8,389	(374)	5,275	(326)
10 – 19	7,983	(327)	6,566	(309)	3,444	(291)
≥ 20	5,214	(408)	3,393	(317)	1,113	(144)

* These distributions apply for both the lung cancer and non-malignant respiratory disease analyses.

† Person-years

‡ Number of workers in final attained category

Table IV.15

Trends of Lung Cancer Mortality by Total Employment Duration and Latency Interval: 2,570 White Males, Lompoc Cohort

Duration of employment (yr)	Latency interval (yr)					
	0		5		15	
	No. deaths	RR† (95% CI)‡	No. deaths	RR† (95% CI)‡	No. deaths	RR† (95% CI)‡
1 - 4 (reference)	20	1.00 (–)	23	1.00 (–)	28	1.00 (–)
5 – 9	12	2.21 (1.07 – 4.54)	10	1.64 (0.77 – 3.49)	10	1.38 (0.66 – 2.90)
10 – 19	9	1.55 (0.68 – 3.53)	10	1.43 (0.66 – 3.08)	13	1.79 (0.89 – 3.60)
≥ 20	18	2.15 (1.12 – 4.11)	16	2.12 (1.09 – 4.12)	8	2.24 (0.95– 5.26)

† Relative risk adjusted for age, calendar year, duration of follow-up, ethnicity (Hispanic vs. non-Hispanic)

‡ 95 percent confidence interval for RR

Table IV.16

Person-years of Observation and Numbers of Workers by Duration of Employment in Dust-Exposed Jobs and Latency Interval: 2,570 White Males, Lompoc Cohort

Duration of employment (yr)	Latency interval (yr) 0		5		15	
< 5 (reference)	38,324†	(1,548)‡	42,828	(1,625)	50,605	(1,877)
5-9	9,497	(361)	7,913	(362)	4,913	(316)
10-19	7,561	(327)	6,120	(305)	3,067	(276)
≥ 20	3,919	(334)	2,441	(251)	716	(101)

*These person-year distributions apply for both the lung cancer and non-malignant respiratory disease analyses

†Person-years

‡Number of workers in final attained category

Table IV.17

Trends of Lung Cancer Mortality by Duration of Employment in Dust-Exposed Jobs by Latency Interval: 2,570 White Males, Lompoc Cohort

Duration of employment (yr)	Latency interval (yr)					
	0		5		15	
	No. deaths	RR† (95% CI)‡	No. deaths	RR† (95% CI)‡	No. deaths	RR† (95% CI)‡
< 5 (reference)	24	1.00 (–)	27	1.00 (–)	31	1.00 (–)
5 – 9	10	1.67 (0.79 – 3.51)	8	1.24 (0.56 – 2.75)	9	1.29 (0.60 – 2.76)
10 – 19	11	1.85 (0.88 – 3.88)	12	1.72 (0.86 – 3.47)	13	2.00 (1.01 – 3.95)
≥ 20	14	2.31 (1.18 – 4.51)	12	2.29 (1.13 – 4.62)	6	2.88 (1.13– 7.33)

† Relative risk adjusted for age, calendar year, duration of follow-up, ethnicity (Hispanic vs. non-Hispanic)

‡ 95 percent confidence interval for RR

Table IV.18

Person-years of Observation and Numbers of Workers, by Duration of Employment in Dust-Exposed Jobs, Weighted by Time Period and Exposure Intensity, and Latency Interval: 2,570 White Males, Lompoc Cohort *

Weighted duration of Employment category†	Latency interval (yr)					
	0		5		15	
< 50 (reference)	33,085‡	(1,570)§	36,984	(1,675)	44,757	(1,803)
50-99	12,304	(491)	10,239	(425)	6,505	(355)
100-199	7,787	(274)	6,708	(250)	4,515	(223)
≥ 200	6,126	(235)	5,371	(220)	3,524	(189)

* These person-year distributions apply for both the lung cancer and non-malignant respiratory disease analyses.

† Exposure intensity score x years

‡ Person-years

§ Number of workers in final attained category

Table IV.19

Trends of Lung Cancer Mortality by Duration of Employment in Dust-Exposed Jobs, Weighted by Time Period and Exposure, by Latency Interval: 2,570 White Males, Lompoc Cohort

Weighted duration of employment*	Latency interval (yr) 0 No. deaths	0 RR† (95% CI)‡	5 No. deaths	5 RR† (95% CI)‡	15 No. deaths	15 RR† (95% CI)‡
< 50 (reference)	19	1.00 (–)	20	1.00 (–)	25	1.00 (–)
50-99	9	0.95 (0.42 – 2.13)	10	1.06 (0.49 – 2.31)	8	0.85 (0.37-1.94)
100-199	10	1.29 (0.58 – 2.85)	9	1.16 (0.51 – 2.62)	7	0.88 (0.37-2.11)
≥ 200	21	2.58 (1.26 – 5.27)	20	2.48 (1.22 – 5.08)	19	2.46 (1.23-4.93)

* Exposure intensity score x years

† Relative risk adjusted for age, calendar year, duration of follow-up, ethnicity (Hispanic vs. non-Hispanic), duration of employment in natural dust-exposed jobs (>5 vs. ≥ 5 yr).

‡ 95 percent confidence interval for RR

Table IV.20

Person-years of Observation and Numbers of Workers, by Estimated Cumulative Exposure to Crystalline Silica and Latency Interval: 2,570 White Males, Lompoc Cohort*

Crystalline silica exposure level†	Latency interval (yr)					
	0		5		15	
< 50 (reference)	32,562‡	(1,512)§	36,789	(1,611)	45,262	(1,749)
50-99	11,721	(471)	9,731	(426)	5,737	(380)
100-199	8,266	(331)	6,886	(298)	4,407	(238)
≥ 200	6,752	(256)	5,895	(235)	3,894	(203)

* These person-year distributions apply for both the lung cancer and non-malignant respiratory disease analyses.

† Exposure intensity score x years

‡ Person-years

§ Number of workers in final attained category

Table IV.21

Trends of Lung Cancer Mortality by Estimated Cumulative Exposure to Crystalline Silica, by Latency Interval: 2,570 White Males, Lompoc Cohort

Crystalline silica exposure level*	Latency interval (yr)					
	0		5		15	
	No. deaths	RR† (95% CI)‡	No. deaths	RR† (95% CI)‡	No. deaths	RR† (95% CI)‡
< 50 (reference)	19	1.00 (–)	20	1.00 (–)	23	1.00 (–)
50-99	6	0.76 (0.30 - 1.90)	6	0.78 (0.31 – 1.94)	8	1.19 (0.52 – 2.73)
100-199	11	1.48 (0.69 - 3.15)	11	1.51 (0.71 – 3.22)	9	1.37 (0.61 – 3.06)
≥ 200	23	2.87 (1.47 – 5.64)	22	2.81 (1.43 – 5.53)	19	2.74 (1.38 – 5.46)

* Exposure intensity score x years

† Relative risk adjusted for age, calendar year, duration of follow-up, ethnicity (Hispanic vs. non-Hispanic)

‡ 95 percent confidence interval for RR

Table IV.22

Trends of Lung Cancer Mortality by Estimated Cumulative Exposure to Crystalline Silica, Assuming a 15-Year Latency, Under Various Exposure Intensity Weighting Schemes: 2,570 White Males, Lompoc Cohort

Crystalline silica exposure level*	Exposure intensity weights					
	1,2,4		1,3,6		1,4,8	
	RR†	(95% CI)‡	RR†	(95% CI)‡	RR†	(95% CI)‡
<50 (reference)	1.00	(–)	1.00	(–)	1.00	(–)
50-99	1.61	(0.74 - 3.53)	1.19	(0.52 - 2.73)	1.40	(0.62 - 3.16)
100-199	1.52	(0.67 - 3.45)	1.37	(0.61 - 3.06)	1.60	(0.70 - 3.63)
≥ 200	2.47	(1.23 - 4.97)	2.74	(1.38 - 5.46)	2.44	(1.22 - 4.85)

* Exposure intensity score x years

† Relative risk adjusted for age, calendar year, duration of follow-up, ethnicity (Hispanic vs. non-Hispanic)

‡ 95 percent confidence interval for RR

Table IV.23

Observed and Expected Deaths and Standardized Mortality Ratios for Non-Malignant Respiratory Diseases by Year of Death, Year of Hire, Time Since First Employment, and Age at Death: 2,570 White Males, Lompoc Cohort

Variable	Person-yrs	Obs	Exp†	SMR	(95% CI)‡
Year of death					
1942-49	3,901	2	0.21	9.50	(1.15 - 34.3)
1950-59	10,227	2	1.01	1.99	(0.24 - 7.18)
1960-69	14,639	7	3.55	1.97	(0.79 - 4.06)
1970-79	16,677	21	7.24	2.90	(1.79 - 4.43)
1980-87	13,905	24	9.61	2.50	(1.60 - 3.72)
Year of hire					
Before 1930	2,048	8	2.45	3.27	(1.41 - 6.45)
1930-39	4,246	12	2.87	4.18	(2.16 - 7.30)
1940-49	21,946	24	10.9	2.21	(1.41 - 3.28)
1950-59	16,837	8	4.48	1.79	(0.77 - 3.52)
1960-69	10,166	3	0.85	3.53	(0.73 - 10.3)
1970-86	4,106	1	0.10	10.2	(0.26 - 57.0)
Time since first employment(yr)					
<10	18,303	3	0.73	4.12	(0.85 - 12.1)
10 - 19	18,184	3	2.35	1.28	(0.26 - 3.73)
20 - 29	13,371	16	5.52	2.90	(1.66 - 4.71)
≥ 30	9,492	34	13.0	2.61	(1.81 - 3.65)
Age at death					
< 40	25,028	2	0.46	4.37	(0.53 - 15.8)
40 - 49	15,052	2	1.21	1.66	(0.20 - 5.99)
50 - 59	11,513	13	4.21	3.09	(1.64 - 5.28)
60 - 69	5,849	12	7.92	1.52	(0.78 - 2.65)
≥ 70	1,907	27	7.83	3.45	(2.27 - 5.02)

† Based on rates for U.S. White Males, 1942-87

‡ 95 percent confidence interval for SMR

Table IV. 24

Non-Malignant Respiratory Diseases by Type, by Year of Death, Year of Hire, Time Since First Employment, and Age at Death: 2,570 White Males, Lompoc Cohort

Variable	Silicosis or Pneumoconiosis*	Other NMRD
Year of death		
1942-49	0	2
1950-59	2	0
1960-69	3	4
1970-79	7	14
1980-87	5	19
Year of hire		
Before 1930	4	4
1930-39	7	5
1940-49	6	18
1950-59	0	8
1960-69	0	3
1970-86	0	1
Time since first employment(yr)		
<10	1	2
10 - 19	0	3
20 - 29	3	13
≥ 30	13	21
Age at death		
< 40	0	2
40 - 49	1	1
50 - 59	2	11
60 - 69	6	6
≥ 70	8	19

*Does not include asbestosis

Table IV.25

Observed and Expected Deaths and Standardized Mortality Ratios for Non-Malignant Respiratory Diseases by Total Duration of Employment and Duration of Employment in Dust-Exposed Jobs: 2,570 White Males, Lompoc Cohort

Variable	Person-yrs	Obs	Exp†	SMR	(95% CI)
Total duration of employment (yr)					
1 - 4	36,028	21	10.4	2.02	(1.25 - 3.08)
5 - 9	10,065	9	2.84	3.17	(1.45 - 6.02)
10 - 19	7,978	14	3.46	4.03	(2.21 - 6.78)
≥ 20	5,238	12	4.90	2.45	(1.27 - 4.28)
Duration of employment in dust-exposed jobs (yr)					
< 5	38,349	23	11.8	1.95	(1.24 - 2.93)
5 - 9	9,503	12	3.00	4.00	(2.07 - 6.99)
10 - 19	7,556	13	3.36	3.87	(2.06 - 6.62)
≥ 20	3,941	8	3.50	2.28	(0.99 - 4.50)

† Based on rates for U.S. White Males, 1942-87

‡ 95 percent confidence interval for SMR

Table IV.26

Trends of Non-Malignant Respiratory Disease Mortality by Total Duration of Employment, by Latency Interval: 2,570 White Males, Lompoc Cohort

	Latency interval (yr)					
	0		5		15	
Duration of employment (yr)	No. deaths	RR† (95% CI)‡	No. deaths	RR† (95% CI)‡	No. deaths	RR† (95% CI)‡
1-4 (reference)	21	1.00 (—)	22	1.00 (—)	23	1.00 (—)
5-9	9	1.55 (0.71 – 3.41)	8	1.45 (0.64 – 3.28)	9	1.51 (0.68 – 3.35)
10-19	14	2.07 (1.02 – 4.22)	14	1.93 (0.95 – 3.91)	15	2.04 (1.01 – 4.09)
≥20	12	1.20 (0.58 – 2.47)	12	1.33 (0.64 – 2.76)	9	1.78 (0.77 – 4.13)

† Relative risk adjusted for age, calendar year, duration of follow-up, ethnicity (Hispanic vs. non-Hispanic)

‡ 95 percent confidence interval for RR

Table IV.27

Trends of Non-Malignant Respiratory Disease Mortality by Duration of Employment in Dust-Exposed Jobs, by Latency Interval: 2,570 White Males, Lompoc Cohort

	Latency interval (yr)					
	0		5		15	
Duration of employment (yr)	No. deaths	RR† (95% CI)‡	No. deaths	RR† (95% CI)‡	No. deaths	RR† (95% CI)‡
<5 (reference)	23	1.00 (—)	24	1.00 (—)	26	1.00 (—)
5-9	12	2.01 (0.99 – 4.05)	11	1.92 (0.93 – 3.96)	11	1.80 (0.87 – 3.74)
10-19	13	2.06 (1.02 – 4.16)	13	1.97 (0.97 – 3.96)	13	1.89 (0.93 – 3.80)
≥20	8	1.17 (0.52 – 2.64)	8	1.32 (0.58 – 3.00)	6	1.82 (0.71 – 4.66)

† Relative risk adjusted for age, calendar year, duration of follow-up, ethnicity (Hispanic vs. non-Hispanic)

‡ 95 percent confidence interval for RR

Table IV.28

Trends of Non-Malignant Respiratory Disease Mortality by Duration of Employment in Dust-Exposed Jobs, Weighted by Time Period and Exposure Intensity, by Latency Interval: 2,570 White Males, Lompoc Cohort

Weighted duration of employment*	Latency interval (yr) 0		5		15	
	No. deaths	RR† (95% CI)‡	No. deaths	RR† (95% CI)‡	No. deaths	RR† (95% CI)‡
< 50 (reference)	15	1.00 (—)	16	1.00 (—)	18	1.00 (—)
50-99	10	1.33 (0.59 - 3.02)	10	1.33 (0.59 - 3.00)	10	1.44 (0.63 - 3.27)
100-199	9	1.35 (0.57 - 3.17)	8	1.20 (0.50 - 2.89)	7	1.13 (0.45 - 2.85)
≥ 200	22	2.44 (1.16 - 5.11)	22	2.43 (1.17 - 5.06)	21	2.63 (1.26 - 5.48)

* Exposure intensity score x years

† Relative risk adjusted for age, calendar year, duration of follow-up, ethnicity (Hispanic vs. non-Hispanic)

‡ 95 percent confidence interval for RR

Table IV.29

Trends of Non-Malignant Respiratory Disease Mortality by Estimated Cumulative Exposure to Crystalline Silica, by Latency Interval: 2,570 White Males, Lompoc Cohort

Cumulative silica exposure level*	Latency interval (yr): 0 No. deaths	0 RR† (95% CI)‡	5 No. deaths	5 RR† (95% CI)‡	15 No. deaths	15 RR† (95% CI)‡
< 50 (reference)	14	1.00 (—)	15	1.00 (—)	19	1.00 (—)
50-99	7	1.29 (0.52 - 3.22)	7	1.32 (0.53 - 3.26)	6	1.13 (0.44 - 2.93)
100-199	12	2.19 (1.00 - 4.79)	11	2.03 (0.91 - 4.51)	9	1.58 (0.69 - 3.63)
≥ 200	23	2.91 (1.41 - 6.00)	23	2.92 (1.42 - 5.99)	22	2.71 (1.35 - 5.46)

* Exposure intensity score x years

† Relative risk adjusted for age, calendar year, duration of follow-up, ethnicity (Hispanic vs. non-Hispanic)

‡ 95 percent confidence interval for RR

Table IV.30

Trends of Non-Malignant Respiratory Disease Mortality by Estimated Cumulative Exposure to Crystalline Silica, Assuming a 15-Year Latency, Under Various Exposure Intensity Weighting Schemes: 2,570 White Males, Lompoc Cohort

Crystalline silica exposure level*	Exposure intensity weights					
	1,2,4		1,3,6		1,4,8	
	RR†	(95% CI)‡	RR†	(95% CI)‡	RR†	(95% CI)‡
< 50 (reference)	1.00	(–)	1.00	(–)	1.00	(–)
50-99	1.14	(0.44 - 2.96)	1.13	(0.44 - 2.93)	1.09	(0.42 - 2.81)
100-199	1.53	(0.66 - 3.56)	1.58	(0.69 - 3.63)	1.47	(0.62 - 3.50)
≥ 200	2.19	(1.10 - 4.35)	2.71	(1.35 - 5.46)	2.18	(1.10 - 4.29)

* Exposure intensity score x years

† Relative risk adjusted for age, calendar year, duration of follow-up, ethnicity (Hispanic vs. non-Hispanic)

‡ 95 percent confidence interval for RR

Table IV.31

Observed and Expected Deaths and Standardized Mortality Ratios for Lung Cancer According to Smoking Status: 2,570 White Males, Lompoc Cohort

Smoking Status	Person-years	Obs	Exp†	SMR	(95% CI)‡
Smokers (N= 768)	16,846	18	8.92	2.02	(1.20 - 3.19)
Non-smokers (N= 345)*	6,010	3	3.19	0.94	(0.19 - 2.74)
Unknown (N=1,457)	36,492	38	29.3	1.30	(0.92 - 1.78)

* Includes 47 pipe or cigar smokers

† Based on rates for U.S. white males, 1942-87

‡ 95 percent confidence interval for SMR

Table IV.32

Observed and Expected Deaths and Standardized Mortality Ratios for Non-Malignant Respiratory Diseases According to Smoking Status: 2,570 White Males, Lompoc Cohort

Smoking Status	Person-years	Obs	Exp	SMR	(95% CI)‡
Smokers (N=768)	16,846	15	4.13	3.63	(2.03 - 5.98)
Non-smokers (N = 345)*	6,010	3	1.86	1.61	(0.33 - 4.71)
Unknown (N = 1,457)	36,492	38	15.6	2.43	(1.72 - 3.34)

* Includes 47 pipe or cigar smokers

† Based on rates for U.S. White males 1942 -87

‡ 95 percent confidence interval for SMR

Table IV.33

Observed and Expected Deaths and Standardized Mortality Ratios for Hispanic (N=533, 12,540 person-years) and Non-Hispanic (N=2,037, 46,781 person-years) White Males, Lompoc Cohort: Selected Causes of Death

Cause of death	Hispanics				Non-Hispanics			
	Obs	Exp†	SMR	(95% CI)‡	Obs	Exp†	SMR	(95% CI)‡
All causes	112	120	0.94	(0.76-1.12)	516	444	1.16	(1.06-1.27)
All cancers	15	26.4	0.57	(0.32-0.94)	117	94.6	1.24	(1.02-1.48)
Lung cancer	3	9.21	0.33	(0.07-0.95)	56	32.2	1.74	(1.31-2.26)
Non-malignant respiratory diseases	8	4.74	1.69	(0.73 - 3.32)	48	16.9	2.84	(2.10-3.77)

†Based on rates for U.S. white males, 1942-87

‡95 percent confidence interval for SMR

Table IV.34

Numbers of Workers by Smoking Status, Estimated Cumulative Exposure to Crystalline Silica, (Lagged 15 Years), and Year of Birth: 2,570 White Males, Lompoc Cohort

Year of birth	Cumulative exposure level*											
	<50			50-99			100-199			≥200		
	Sm	Non-Sm	Unk	Sm	Non-Sm	Unk	Sm	Non-Sm	Unk	Sm	Non-Sm	Unk
Before 1890	0	0	6	0	0	0	0	0	1	0	0	4
1890-99	1	2	42	0	2	11	2	0	7	4	0	23
1900-09	5	5	83	3	2	23	5	0	30	17	7	33
1910-19	33	9	211	12	0	51	14	5	59	21	5	45
1920-29	65	17	277	28	6	94	19	7	48	18	4	15
1930-39	115	24	129	46	15	23	18	4	14	2	2	3
1940-49	160	75	102	37	9	18	2	1	2	0	0	0
1950-59	109	107	85	0	0	0	0	0	0	0	0	0
≥1960	32	37	18	0	0	0	0	0	0	0	0	0
Total	520	276	953	126	34	220	60	17	161	62	18	123

*Exposure intensity score x years

Table IV.35
Smoking Status by Estimated Cumulative Exposure to Crystalline Silica
Lagged 15 Years: 2,570 White Males, Lompoc Cohort

Cumulative silica exposure level*	Smoking Status					
	Smokers		Non-smokers		Unknown	
	No.	(%)†	No.	(%)†	No.	(%)‡
< 50 (reference)	520	(65.3)	276	(34.7)	953	(54.5)
50-99	126	(78.8)	34	(21.2)	220	(57.9)
100-199	60	(77.9)	17	(22.1)	161	(67.6)
≥ 200	62	(77.5)	18	(22.5)	123	(60.6)
Total	768	(69.0)	345	(31.0)	1,457	(56.7)

* Exposure intensity score x years

† Percent of workers with known smoking status within exposure level group

‡ Percent of total workers in exposure level group

Table IV.36

Smoking Status by Estimated Cumulative Exposure to Crystalline Silica Lagged 15 Years: Lompoc Cohort, 1,765 White Males Born 1890-1939

Cumulative silica exposure level*	No. workers with smoking data	No. of Smokers	Percent smokers: Crude	Percent smokers: Adjusted to birth year of cohort†	Percent smokers: Adjusted to birth year of workers with smoking data‡
< 50 (reference)	276	219	79.3	73.9	77.3
50-99	114	89	78.1	78.4	79.2
100-199	74	58	78.4	79.9	79.5
≥ 200	80	62	77.5	74.1	67.9

* Exposure intensity score x years

† Adjusted to birth year distribution of all 1,765 white males born 1890-1939

‡ Adjusted to birth year distribution of 544 whites with available smoking data born 1890-1939.

Table. IV.37

Trends of Lung Cancer Mortality by Estimated Cumulative Exposure to Crystalline Silica, Assuming a 15-Year Latency: Lompoc Cohort, 1,765 White Males Born 1890-1939

Cumulative exposure Level	No. deaths	Person-Years	RR†	(95% CI)‡
< 50 (reference)	22	34,700	1.00	(—)
50–99	8	5,489	1.21	(0.52–2.78)
100-199	9	4,390	1.37	(0.61–3.08)
≥ 200	18	3,835	2.67	(1.32–5.41)

* Exposure intensity score x years

† Relative risk adjusted for age, calendar year, duration of follow-up, ethnicity (Hispanic vs. non-Hispanic)

‡ 95 percent confidence interval for RR

Table. IV.38

Observed and Expected Mortality for Lung Cancer According to Estimated Cumulative Exposure to Crystalline Silica, Assuming a 15-Year Latency Among White Male Cigarette Smokers (N=768): Lompoc, Cohort

Crystalline silica exposure level*	Person-years	Obs	Exp†	SMR	(95% CI)‡
< 50	13,398	4	4.20	0.95	(0.26–2.44)
50–99	1,260	3	1.29	2.33	(0.48–6.80)
100–199	1,075	4	1.52	2.62	(0.72–6.72)
≥ 200	1,099	7	1.91	3.67	(1.48–7.57)

* Exposure intensity score x years

† Based on rates for U.S. white males, 1942–87

‡ 95 percent confidence interval for SMR

Table IV.39

Proportions Distributions of Smokers Required to Eliminate Observed Exposure-Response Trend for Crystalline Silica Exposure and Lung Cancer, Assuming a 15-Year Latency and a Relative Risk of 10 for Smoking

Cumulative silica exposure level*	Observed RR**	Proportion of smokers in reference group†		
		0.30	0.40	0.50
< 50 (reference)	1.00	0.30	0.40	0.50
50-99	1.19	0.38	0.50	0.62
100-199	1.37	0.45	0.59	0.73
≥ 200	2.74	[1.02]‡	[1.29]‡	[1.56]‡

* Exposure intensity score x years

** From data in Table IV.21

† Proportion of smokers required in exposure category to reduce observed RR to 1.00

‡ [ ] number larger than 1.00 impossible

Table IV.40
Ethnicity by Estimated Cumulative Exposures to Crystalline Silica
Lagged 15 Years: 2,570 White Males, Lompoc Cohort

Cumulative silica exposure level*	Ethnic group			
	Hispanics		Non-Hispanics	
	No.	(%)†	No.	(%)†
< 50 (reference)	342	(19.6)	1,407	(80.4)
50-99	89	(23.4)	291	(76.6)
100-199	52	(21.8)	186	(78.2)
≥ 200	50	(24.6)	153	(75.4)
Total	533	(20.7)	2,037	(79.3)

* Exposure intensity score x years

† Percent of workers within exposure level group

Table IV.41

Trends of Lung Cancer Mortality by Estimated Cumulative Exposure to Crystalline Silica, Assuming a 15-Year Latency: 2,037 Non-Hispanic White Males, Lompoc

Cumulative silica exposure level*	No. of Deaths	Person-years	RR†	(95% CI)‡
< 50 (reference)	20	36,308	1.00	(—)
50–99	8	4,261	1.38	(0.59-3.21)
100-199	9	3,357	1.59	(0.69-3.62)
≥ 200	19	2,845	3.25	(1.59-6.67)

* Exposure intensity score x years

† Relative risk adjusted for age, calendar year, duration of follow-up

‡ 95 percent confidence interval for RR

Table IV.42

Standardized Mortality Ratios for Lung Cancer and Non-Malignant Respiratory-Diseases Under Different Treatments of Unknown Vital Status: 2,570 White Males, Lompoc Cohort

		Vital status assumption			
		Unknowns alive as of last contact		Unknowns alive as of 1 Jan. 1988	
Cause of death	Obs	SMR†	(95% CI)‡	SMR†	(95% CI)‡
Lung cancer	59	1.43	(1.09 - 1.84)	1.15	(0.88 - 1.49)
Non-malignant respiratory diseases	56	2.59	(1.96 - 3.36)	1.99	(1.51 - 2.59)

† Based on rates for U.S. white males, 1942-87

‡ 95 percent confidence interval for SMR

Table IV.43

Standardized Mortality Ratios for Lung Cancer, Under Different Treatments of Unknown Vital Status, by Duration of Employment in Dust-Exposed Jobs: 2,570 White Males, Lompoc Cohort

	Vital status assumption			
	Unknowns alive as of last contact*		Unknowns alive as of 1 Jan. 1988	
Duration of employment (yr)	SMR†	(95% CI)‡	SMR†	(95% CI)‡
<5	1.01	(0.65 - 1.51)	0.75	(0.48 - 1.12)
5 - 9	1.77	(0.85 - 3.25)	1.54	(0.74 - 2.84)
10 - 19	1.92	(0.96 - 3.43)	1.80	(0.90 - 3.22)
≥ 20	2.28	(1.23 - 3.76)	2.16	(1.18 - 3.62)

* From Table IV.13

† Based on rates in U.S. white males, 1942 - 87

‡ 95 percent onfidence interval for SMR

Table IV.44
Standardized Mortality Ratios for Non-Malignant Respiratory-Diseases, Under Different Treatments of Unknown Vital Status, by Duration of Employment in Dust-Exposed Jobs: 2,570 White Males, Lompoc Cohort

	Vital status assumption			
	Unknowns alive as of last contact*		Unknowns alive as of 1 Jan. 1988	
Duration of employment (yr)	SMR†	(95% CI)‡	SMR†	(95% CI)‡
< 5	1.95	(1.24 - 2.93)	1.34	(0.85 - 2.02)
5 - 9	4.00	(2.07 - 6.99)	3.39	(1.75 - 5.92)
10 - 19	3.87	(2.06 - 6.62)	3.56	(1.90 - 6.10)
≥ 20	2.28	(0.99 - 4.50)	2.11	(0.91 - 4.16)

* From Table IV.25
† Based on rates for U.S. white males, 1942 - 87
‡ 95 percent confidence interval for SMR

Table IV.45

Vital Status and Cause of Death Determination for 104 Asbestos-Exposed White Males: Lompoc Workers*

Vital Status	No.	(%)
Alive as of 1 Jan. 1988	84	(80.8)
Dead — total	14	(13.5)
— with certificate	14(100)†	
— without certificate	0 (0)†	
Unknown	6	(5.7)
Total	104	

* 2,339 person-years

† Percent of total identified deaths

Table IV.46

Observed and Expected Deaths and Standardized Mortality Ratios for Selected Causes of Death: 104 Asbestos-Exposed White Males, Lompoc Workers*

Cause of death	Obs	Exp†	SMR	(95% CI)‡
All causes combined	14	14.9	0.94	(0.52 - 1.58)
All cancers	5	3.22	1.55	(0.50 - 3.62)
Lung cancer	4	1.13	3.54	(0.96 - 9.05)
Non-malignant respiratory diseases	1	0.51	1.97	(0.05 - 11.0)

* 2,339 person years

† Based on rates for U.S. white males, 1942-87

‡ 95 percent confidence interval for SMR

Table IV.47
Vital Status and Cause of Death Determination for
37 Black Male Lompoc Workers*

Vital Status	No.	(%)
Alive as of 1 Jan. 1988	35	(94.6)
Dead — total	1	(2.7)
— with certificate	1 (100)†	
— without certificate	0 (0)†	
Unknown	1	(2.7)
Total	37	

* 362 person-years
† Percent of total identified deaths

Table IV.48

Observed and Expected Deaths and Standardized Mortality Ratios for Selected Causes of Death: 37 Black Males, Lompoc Workers

Cause of death	Obs	Exp†	SMR	(95% CI)‡
All causes combined	1	2.81	0.36	(0.09 - 0.20)
All cancers	1	0.52	1.92	(0.05 - 10.7)
Lung cancer	1	0.19	5.23	(0.13 - 28.1)
Non-malignant respiratory diseases	0	0.13	0	(0 - 28.0)

† Based on rates for U.S. non-white males, 1942-87

‡ 95 percent confidence interval for SMR

Table IV.49
Vital Status Tracing and Cause of Death Determination for
242 White Female Lompoc Workers*

Vital Status	No.	(%)
Alive as of 1 Jan. 1988	190	(78.5)
Dead — total	31	(12.8)
— with certificate	31 (100)†	
— without certificate	0 (0)†	
Unknown	21	(8.7)
Total	242	

* 4,461 person-years
† Percent of total identified deaths

Table IV.50

Observed and Expected Deaths and Standardized Mortality Ratios for Selected Causes of Death: 242 White Females, Lompoc Workers

Cause of death	Obs	Exp†	SMR	(95% CI)
All causes combined	31	21.5	1.44	(0.98 - 2.05)
All cancers	12	7.10	1.69	(0.87 - 2.95)
Lung cancer	3	1.09	2.76	(0.57 - 8.06)
Non-malignant respiratory diseases	5	0.64	7.77	(2.52 - 18.1)

† Based on rates for U.S. white females, 1942-87

Table IV.51
Vital Status Tracing and Cause of Death Determination for
158 White Male Basalt Plant Workers*

Vital Status	No.	(%)
Alive as of 1 Jan. 1988	119	(75.3)
Dead — total	32	(20.3)
— with certificate	26	(81.3)†
— without certificate	6	(18.7)†
Unknown	7	(4.4)
Total	158	

* 3,015 person-years

† Percent of total identified deaths

Table IV.52

Observed and Expected Deaths and Standardized Mortality Ratios for Selected Causes of Death: 158 White Male Basalt Plant Workers

Cause of death	Obs	Exp†	SMR	(95% CI)‡
All causes combined	32	28.0	1.14	(0.78 - 1.61)
All cancers	8	6.50	1.23	(0.53 - 2.42)
Lung cancer	4	2.37	1.69	(0.46 - 4.38)
Non-malignant respiratory diseases	0	1.12	0	(0 - 3.30)

† Based on rates for U.S. white males, 1942-87

‡ 95 percent confidence interval for SMR

Table IV.53

Vital Status Tracing and Cause of Death Determination for 121 White Male Quincy, Washington Plant Workers*

Vital Status	No.	(%)
Alive as of 1 Jan. 1988	115	(95.0)
Dead — total		
— with certificate	6 (100)†	(5.0)
— without certificate	0 (0)†	
Unknown	0	(0)
Total	121	

* 997 person-years

† Percent of total identified deaths

Table IV.54

Observed and Expected Deaths and Standardized Mortality Ratios for Selected Causes of Death: 121 Quincy, Washington Plant Workers

Cause of death	Obs	Exp†	SMR	(95% CI)‡
All causes combined	6	4.97	1.21	(0.44 - 2.63)
All cancers	0	1.08	0	(0 - 3.41)
Lung cancer	0	0.39	0	(0 - 9.42)
Non-malignant respiratory diseases	0	0.22	0	(0 - 16.9)

† Based on rates for U.S. white males, 1970-87

‡ 95 percent confidence interval for SMR

CHAPTER V

DISCUSSION AND CONCLUSIONS

This study was initiated because of concerns raised by IARC's classification of crystalline silica as a probable human carcinogen. Our research objectives were to examine the historical mortality patterns among DE workers, and to evaluate whether observed disease excesses were related to workplace exposures in this industry. In particular, we focused most attention on lung cancer and non-malignant respiratory diseases (NMRD) and their possible associations with cumulative exposures to crystalline silica. Although prior epidemiologic evidence regarding the carcinogenicity of crystalline silica provided the scientific backdrop for the study, we have not explicitly tested the hypothesis that crystalline silica is a human carcinogen. Instead, we regard the findings from this investigation as specifically pertinent to dust exposures in the DE industry. Conclusive answers to the broader scientific questions regarding the carcinogenic effects of crytalline or amorphous silica, and the possible intervening role of pulmonary fibrosis, cannot be determined from this study, although this study provides valuable new information.

The most important findings from the study were overall increases in mortality from lung cancer (SMR=1.43) and NMRD (SMR=2.59) when the main study cohort, consisting of 2,570 Lompoc white males, was compared with the national population, and apparent dose-response trends for both lung cancer and NMRD with cumulative exposure to crystalline silica. In evaluating whether these findings are supportive of cause-effect associations, it is necessary to consider competing explanations for the data, principally whether the observed relationships between DE exposure and mortality from lung cancer and NMRD were the result of bias. Interpretations of the findings are also aided by placing this study's findings in context with results of previous research.

The following discussion is divided into three sections. The first summarizes our evaluations of the relative strengths and limitations of the study; the second addresses the possible extent of bias that may have distorted the study findings; and the third section contains our interpretations of the data and accompanying conclusions.

A. Strengths and Limitations of the Study

The main strengths of this research were the ability to track the long-term mortality experience of the cohort, and to link mortality risk patterns with estimated cumulative dust exposure indices. The main study cohort was followed for over 40 years, and the average duration of follow-up was nearly 25 years. Thus, there was a sufficiently long period of observation to assess risks from cancer and other chronic diseases. The assessment and analysis of complete work history data for the Lompoc workers was an important component of the study in that it permitted a reasonably comprehensive examination of dose-response relationships. Most of the prior research of crystalline silica-exposed cohorts have been forced to rely on very crude indicators of exposure, typically cumulative employment duration, which can be a poor dose surrogate. Also, our assessments of dose-response involved internal comparisons among subcohorts classified according to exposure level. By using internal comparisons, we minimized some of the biases, such as the Healthy Worker Effect, that can arise in analyses that are based strictly on comparisons against national or regional populations.

The study suffered from some notable limitations, including incomplete cohort enumeration, a less than complete ascertainment of vital status and cause of death information, the absence of quantitative and representative industrial hygiene exposure data spanning all years of the cohort's employment, and the absence of complete and valid data on cigarette smoking, which is the main candidate confounding variable. The possibility of confounding by smoking will be considered in detail in the discussion on bias.

Undoubtedly, the cohort that was identified for study was incomplete because personnel records were not available (misplaced or lost) at the time of cohort enumeration. We are not aware of the extent of cohort incompleteness because alternative sources, such as Internal Revenue Forms (941A) [Marsh and Enterline, 1979], were not sought for review. Nonetheless, incomplete cohort enumeration does not in itself cause bias. Incomplete cohort enumeration can only produce bias when the reasons for under-ascertainment are related to both exposure and disease risks (e.g., under-ascertainment of heavily exposed workers who were at increased lung cancer risk). There is no reason to believe that this was the case in this study. The cohort can therefore be regarded as a sample of all DE workers employed for at least 12 months in the plants studied. Insofar as personnel records were well maintained at the Lompoc plants, cohort enumeration was probably very close to complete. It may be worthwhile in the future to estimate cohort completeness using alternative data sources.

A vital status tracing rate of 91 percent is less than desired (95 percent or greater). As discussed in Chapter IV, the 91 percent tracing rate may have caused slightly inflated SMRs relative to the national and regional populations because counting of person-years of observation was ended at dates of last contact for workers with unknown vital status. However, this inflation was partially offset by the failure to determine cause of death for 6 percent of deaths, which resulted in slightly under-estimated cause-specific SMRs. The internal comparisons among cohort subgroups, which we regard as more valid and hence more meaningful than comparisons with the U.S. or regional populations, included control for duration of follow-up, thus further minimizing potential bias.

The available industrial hygiene data were insufficient to permit quantitative estimates of workers' exposures in units commonly used in occupational health research (e.g., mg/M^3 x years). The main reason for this was that monitoring data were not available for the early years of employment, especially during the 1930s and 1940s when dust levels were probably much higher than since 1950. Furthermore, many of the dust measurements obtained were for area samples that may not represent workers' actual exposures. An added complication is that most measurements were made with the impinger device rather than by current gravimetric techniques. Conversions from the older units (million particles per cubic foot) to gravimetric units (mg/M^3) would have been required. We made progress in a preliminary sampling study to develop conversion factors [Montgomery et al., 1991], but much more sampling would be needed before statistically reliable conversion factors could be developed for use in the epidemiologic analysis.

As a consequence of the lack of quantitative exposure data, the scheme for estimating cumulative dust exposures is inherently flawed. Uncertainty in the crystalline silica index that was devised for this study is due to possible error in the assignment of exposure intensity weights by job type and time period, and errors in the assumptions regarding the effectiveness of respiratory protection devices. Although the crystalline silica exposure index was based on informed best judgment, the study can be criticized by the amount of uncertainty in this variable. In contrast, duration of employment in the industry at large can be determined with minimal error, but this exposure index is of less scientific interest than one which estimates cumulative crystalline silica. We were somewhat reassured that the trends of risk with crystalline silica exposure are reliable because the exposure-response gradients for lung cancer and NMRD did not fluctuate wildly in the sensitivity analyses when alternative exposure intensity weights were substituted for the "best estimate" weights.

B. The Potential for Bias

Bias in epidemiologic studies can take one of three general forms: selection bias, information bias (i.e., misclassification of exposure or disease), or confounding. These are considered in turn.

The most commonly acknowledged selection bias in occupational epidemiology research is the Healthy Worker Effect (HWE). The HWE is caused by inappropriate comparisons of a worker cohort with an external national or regional reference population. This is most evident for diseases strongly associated with selection for work (e.g., cardiovascular diseases), and to a lesser extent for cancers [McMichael, 1976]. The choice of external reference population, typically national vs. local populations, can have a profound effect on the interpretation of results if there are large regional differences in disease rates. It is noteworthy that this was not the case for lung cancer in the present study, as the SMR remained elevated when either local county or regional rates were used for comparison (see Table IV.11). In general, the HWE can be minimized substantially by making internal comparisons among subgroups of the cohort, as we have done in the exposure-response trend analyses.

Misclassification of exposure or disease status is another potential source of bias. Misclassification can be regarded as either differential or non-differential. For example, exposure misclassification is non-differential if the misclassification resulting from incorrect exposure estimation is the same for workers with and without specific diseases. Likewise, disease status would be non-differentially misclassified if diagnoses were equally erroneous across exposure levels. Differential misclassification occurs when the converse of these situations apply.

Non-differential misclassification of exposure is much more likely to have occurred than differential misclassification because exposure assignment was made without knowledge of workers' health status (e.g., the same for lung cancer and NMRD deaths as for all other workers). It is well known that in an epidemiologic study, non-differential misclassification causes attenuation of observed associations, based on simple exposed vs.

non-exposed contrasts, or in relation to dose-response trends [Rothman, 1986]. The phenomenon of non-differential misclassification bias resulting in a weakened observed association can be thought of as the consequence of an impaired ability to distinguish fully the "signal from the noise" in the data. Noise in the present context occurs from the failure to estimate crystalline silica exposures precisely. Thus, it could be argued that the observed effects of crystalline silica, in particular, may actually be underestimates of the true effects.

As mentioned earlier, it would have been preferable had we been able to reconstruct detailed quantitative exposure estimates for all cohort members. This would have permitted more precise quantification of dose-response relationships, and would have reduced misclassification bias. Instead, we relied on imperfect dose surrogates. Despite the likelihood of non-differential misclassification of exposures, consistent and reasonably strong gradients for both lung cancer and NMRD were detected.

Misclassification of data on lung cancer mortality was unlikely to have occurred in this study because death certificate information was coded by the nosologist without knowledge of exposure status. There is only a remote possibility that the original death certificate recording of lung cancer as underlying cause of death by physicians or coroners was influenced by suspicions that workplace exposure was the cause among DE workers. On the other hand, the original death certificate recording of pneumoconiosis or silicosis as the underlying cause of death could have been influenced by knowledge of DE employment, particularly in the early years of the study when the prevalence of silicosis was probably much greater than during the past 30 years. We do not know whether this occurred.

We have devoted considerable attention to the possibility that the results from the study were attributable to confounding. There were two categories of confounders that could have biased the results. The first are confounders that were measured: gender, race, age, calendar year, and duration of follow-up. Separate analyses were performed by gender/race groups, which precluded confounding by these factors. The data analysis also included statistical control for age, calendar year, and duration of follow-up, thus minimizing the potential for confounded comparisons between exposure categories.

The second set of confounders are factors that were imperfectly or incompletely measured, including Hispanic ethnicity, occupational asbestos exposure, and cigarette smoking. Hispanic ethnicity is a relevant variable because lung cancer rates [Samet et al., 1988] and cigarette smoking habits [Humble et al., 1985; Marcus and Crane, 1985] have been found to be lower among Hispanic than non-Hispanic white males in the U.S. It was possible to classify the cohort according to Hispanic ethnicity using surnames as the indicator of ethnicity. Undoubtedly, the classification was imperfect. Nevertheless, the Lompoc cohort included a larger proportion of Hispanics than the national population, which suggest that the overall SMR for lung cancer (1.43) may underestimate the cohort's excess. The lung cancer SMR (1.59) that was based on comparisons between rates in the cohort and rates in the regional county populations, which have proportionately larger Hispanic populations than the entire U.S., may be more valid. There was only a weak correlation between ethnicity and crystalline silica exposure. Control of confounding by Hispanic ethnicity was attempted by including this factor in the internal rate analyses. As such, the internal rate comparisons were probably only influenced by ethnic status to a small extent.

Asbestos exposure occurred in some areas of the plants, and thus should be regarded as a potential confounder. Accordingly, we eliminated from the main analysis cohort workers with potential past asbestos exposures encountered in the various processes where asbestos was handled. Therefore, to the extent that the work history information permitted, we have diminished the likelihood that asbestos exposure confounded the study results. However, we did not have available work history data that spanned periods of employment before and after employment in the DE industry. Therefore, there may have been some confounding by other occupational exposures, notably lung carcinogens (e.g., asbestos, polycyclic aromatic hydrocarbons, arsenic). There is no reason to suspect that these other exposures were correlated with DE dust exposure levels in the internal exposure-response comparisons, and thus the probable extent of confounding is small.

Cigarette smoking was the main concern as a potential confounder in this study. We evaluated the potential for confounding by cigarette smoking using a variety of "indirect" and "direct" methods. The indirect approaches involved assessing risks for smoking-related diseases other than lung cancer and NMRD, and hypothetical calculations of the extent of correlation between smoking and crystalline silica exposure that would have been required to produce a spurious exposure-response gradient for lung cancer. The patterns of results in both instances indicate that smoking was unlikely to have accounted fully for the observed associations between dust exposure with lung cancer.

The more direct approaches involved analyzing the data for the 1,113 of the 2,570 members of the Lompoc cohort for whom smoking data were available. This was done by examining the correlation between smoking and crystalline silica exposure level, and by performing a separate exposure-response analysis among workers identified as cigarette smokers. Among the 1,113 workers for whom smoking data were available, smoking prevalence appeared to be lowest in the lowest stratum of crystalline silica exposure (assuming a 15-year latency). However, there was no relationship between smoking and exposure among the subset of 544 workers born between 1890 and 1939 and for whom smoking information was available. A separate exposure-response analysis of lung cancer in relation to crystalline silica for all workers (1,745) born between 1890 and 1939 yielded a very similar risk gradient to that observed for the entire Lompoc cohort. The absence of any apparent association between smoking prevalence and crystalline silica exposure in workers born between 1890 and 1939, together with the consistency of exposure-response trends, suggest again that smoking is an improbable explanation for the entire relationship between exposure and lung cancer.

On balance, our examinations of the possible extent of confounding by smoking consistently indicate that smoking is unlikely to be the sole explanation for the findings. Moreover, the available data suggest that the distribution of smoking in the Lompoc cohort could only produce a small amount of confounding bias. However, the amount and detail of the smoking data that were available to us are certainly less than would have been desired for a full accounting of the influence of smoking on lung cancer and NMRD mortality risks. In addition to the incompleteness of the smoking prevalence data in the cohort, we had no information on other facets of cigarette smoking, such as changes in smoking habits over time, the number of cigarettes smoked per day, and the types of cigarettes smoked (filter vs. non-filter), all of which are etiologically important. Thus, for example, there may have been differences in the intensity of smoking (cigarettes per day) between exposure groups, despite apparently similar distributions of smokers and non-smokers. In the absence of detailed data, we cannot discount the possibility of some degree of confounding by these unmeasured smoking-related characteristics.

C. Interpretations and Conclusions

The lung cancer and NMRD results will be discussed separately because of the significant differences in case detection and diagnostic specificity of the two. Also, the potential etiologic relationships with dust for these two disease categories undoubtedly differ.

As summarized in the foregoing discussion, there are neither strong theoretical arguments nor empirical evidence that the associations between DE dust exposure and lung cancer mortality are artifacts caused by bias. We cannot completely discount the possibility that some residual (unmeasured) confounding from cigarette smoking, in particular, caused the risk estimates to be biased to some extent. Nonetheless, we conclude that cigarette smoking was not the sole cause of the lung cancer excess in the cohort, nor could smoking patterns have accounted fully for the observed gradient of risk by cumulative exposure level.

When reviewing the lung cancer findings, one may speculate whether DE exposure or some other factor(s), notably cigarette smoke, was the greater contributor to risk. A related question is whether DE exposure, even in large amounts, can induce lung cancer in the absence of cigarette smoke exposure. Thus, it would be of great interest to determine the independent (sole) and combined effects of DE exposure and smoking on lung cancer risk. The inadequacy of the smoking data precludes explicit answers to these questions. Nevertheless, it is perhaps useful to consider an explanation for the following hypothetical, but not unrealistic situation. If all of the lung cancer deaths in the study had in fact been cigarette smokers, then it could be concluded that long-term, intense DE exposures increased the risk of lung cancer already imparted by smoking.

The remaining competing explanations for the study findings are: that the results were due to chance, or that they reflect the true underlying etiologic relationships. Chance can never be discounted in any study, epidemiologic or otherwise. Consequently, a determination of chance vs. causation must be based on an assessment of the weight and consistency of the evidence in favor of causation. Some important considerations that bear on the assessment of causation in a given study are the consistency of findings within the study and the consistency of findings of the study with those from previous related research [Hill, 1965]. The ability to demonstrate a dose-response relationship, particularly for associations that were predicted a priori, can also improve one's confidence that a statistical relationship reflects a true biological relationship.

The findings for lung cancer in this study were generally consistent with findings from previous studies of cohorts exposed to crystalline silica. The prior epidemiologic studies of most relevance to this investigation are those of workers in the granite, stone, and silica brick industries where crystalline silica is the principal risk factor, and confounding from exposures to other carcinogens (e.g., radon, polycyclic aromatic hydrocarbons) is believed to be nonexistent or minimal. Reference to Table V.1, which lists some of the lung cancer findings summarized previously in Chapter II, indicates that the excesses of lung cancer mortality observed in the present study are generally consistent with those in the published literature. The overall SMR for the Lompoc cohort, 1.43, lies in the range of observed relative risk estimates.

The relatively wide variations in lung cancer risks seen among crystalline silica-exposed cohorts (Table V.1) is to be expected in view of the differences in study populations and exposure types and levels. In fact, as can be seen from Table V.2, observed lung cancer risks among asbestos-exposed cohorts vary quite dramatically. Undoubtedly, differences in asbestos fiber type and exposure levels account for some of the variability. Smaller and less variable relative risks have been observed in cohort studies of workers engaged in the manufacture of fiberglass and other man-made mineral fibers (Table V.3).

The present study was also internally consistent, to a large extent, in that excess lung cancer risks were observed for all groups except the Witco (Quincy, WA) cohort, which has not been followed long enough to yield meaningful data.

Among the Lompoc cohort, we observed generally increasing trends of lung cancer risk with increasing exposure, particularly when duration of dust exposure or crystalline silica exposure was regarded as the dose index. In principle, the steepest exposure-response trend is the most valid indicator of association, provided that there really is an underlying association. This is because the most valid exposure index is the one that is estimated with the least amount of misclassification, and thus its exposure-response trend with disease should be attenuated to a lesser extent than trends based on other exposure indices. Our prior expectation was that the crystalline silica content of DE dust is the most etiologically important aspect of exposure. However, the observed risk gradients for lung cancer with duration of dust exposure and estimated cumulative crystalline silica exposure were not appreciably different. The explanation may be that the exposure assessment for crystalline silica level was fraught with error, perhaps due to faulty assumptions regarding exposure intensity weights, percent crystalline silica content in the various product mixes, or the effectiveness of respiratory protection programs. Alternatively, the total amount of dust exposure, irrespective of crystalline silica content, may be the most etiologically significant exposure factor. Limitations in the industrial hygiene data and the small number of workers exposed only to non-calcined DE do not permit resolution of this question. Further follow-up of DE-exposed workers and improved exposure assessment that takes advantage of data from ongoing industrial hygiene monitoring programs should shed light on this issue.

A straightforward and, in our view, defensible summary interpretation of the lung cancer results is that the excess risk among DE workers is most likely attributable to exposures that occurred before the 1950s. Support for this conclusion derives from the observation of risk gradients that increased with cumulative dust exposure, and the knowledge of substantially higher dust levels during the 1930s and 1940s than in more recent years [Cooper and Cralley, 1958]. It is also noteworthy that there has been no excess of lung cancer among workers hired since 1960 (see Table IV.12), although these workers, as a group, have not yet reached the peak ages of lung cancer risk. Certainly, further follow-up of these recently hired workers will reveal whether lung cancer risk among DE workers has indeed been reduced to baseline risks experienced by the population at large.

Interpreting the NMRD results is more complicated than interpreting the lung cancer findings. The principal source of complication is the heterogeneity of the diseases included in the NMRD category. As mentioned in several places in this report, death certificates are notoriously poor sources of information about specific non-malignant respiratory diseases. There is clear documentation that silicosis was an important health hazard in the early years of the DE industry [Cooper and Cralley, 1958; Cooper and Sargent, 1984]. Insofar as silicosis, by definition, is only caused by silica exposure, and is not a cause of mortality among persons not occupationally exposed, the excess of NMRD in the cohort is not surprising. As with lung cancer, there appeared to be dose-response relationships between DE dust exposure and NMRD mortality, and the strongest gradients were detected for cumulative crystalline silica exposure, which agrees with prior expectation. In fact, the dose-response trends for NMRD probably underestimated the true exposure effects on silicosis because of misclassification introduced by combining silicosis with other chronic non-malignant respiratory diseases in the analysis. Clearly, a proper accounting of the risks of silicosis and other forms of NMRD will require studies that incorporate radiographic and other clinical diagnostic information.

The issue of cigarette smoking as a confounder is more pertinent for emphysema and chronic bronchitis than for silicosis, which is only caused by silica dust, although smoking conceivably could have acted as a confounder for silicosis by exacerbating lung disease and contributing to mortality risk. As with the associations between exposure and lung cancer, there is little evidence on either theoretical or empirical grounds that cigarette smoking among the workers could have been the sole explanation for the overall excess of NMRD mortality or for the observed exposure-response gradients.

The temporal pattern of silicosis mortality (Table IV.24), albeit based on death certificate data, indicates that there have been no fatal cases among workers hired since 1950. As such, reductions in dust exposures appear to have been successful in reducing silicosis risk in the DE industry. At a minimum, analyses of the available radiographic data will be needed to determine whether the time-course of silicosis reveals a true reduction or disappearance of morbidity.

The conclusions of the study are summarized as follows:

1. There have been excesses of lung cancer and non-malignant respiratory disease (NMRD) mortality among DE workers compared to the national and regional populations.

2. The estimated dose-response trends for lung cancer and NMRD with DE dust exposure, especially the crystalline silica content of the dust, are consistent and reasonably strong, and thus indicate a causal role of occupational exposures.

3. It is unlikely that confounding by cigarette smoking can fully explain the overall lung cancer and NMRD excesses or the apparent dose-response trends. Confounding by either asbestos exposure or Hispanic ethnicity is also an unlikely explanation for the results.

4. Relatively intense exposures that occurred before the 1950s were probably the most important occupational contributors to the excess lung cancer and NMRD risks.

5. The time trends of lung cancer and NMRD mortality suggest risk reductions, possibly due to improvements in dust control.

6. Further mortality follow-up of the cohort, accompanied by the accumulation of more detailed exposure and smoking data, will be needed to determine the extent to which exposure abatement efforts have been successful in diminishing mortality risks.

7. The long-term trend of silicosis occurrence and its relationship with dust exposure control measures will require cohort analyses of workers' x-ray and exposure data. This would also permit an examination of the relationship between silicosis and lung cancer risk.

Table V.1

Lung Cancer Relative Risks from Some Cohort Studies of Workers Exposed to Crystalline Silica, but Not Other Lung Carcinogens*

Author (year)	Industry	No. workers in cohort	Relative risk	
			Overall	Highest exposed
Steenland (1986)	Granite	1,905	1.19	1.08
Costello (1988)	Granite	5,414	1.16	1.82
Mehnert (1990)	Granite	2,483	1.09	1.57
Koskela (1990)	Granite	1,026	1.56	2.26
Guenel (1989)	Slate quarry	2,071	2.00	8.08
Puntoni (1988)	Refractory brick	231	1.83	Not given
Merlo (1991)	Refractory brick	1,022	1.51	2.01
Present study (1991)	Diatomaceous earth	2,570†	1.43	2.74‡

† Lompoc cohort white males

‡ Workers in the highest category of estimated crystalline silica exposure lagged 15 years

Table V.2

Lung Cancer Relative Risks from Some Published Studies of Asbestos-Exposed Cohorts

Author (year)	Location/ industry	No. workers in cohort	Relative risk: Overall	Relative risk: Highest exposed†	Comments
Selikoff (1979)	U.S., Canada/ insulation	17,800	4.06	4.24	Exposure type, level not stated; highest ≥20 since exposure onset
Acheson (1984)	England/ amosite	4,820	2.10	4.25	Highest: ordinal ranking
Seidman (1986)	New Jersey/ amosite	820	4.97	11.7	Highest ≥250 f/cc x yr
Dement (1983)	South Carolina/ textile	1,261	3.15	18.2	Chrysotile; highest ≥100,000 f/cc x days
McDonald (1980)	Quebec/ mining	10,939	1.25	2.25	Chrysotile; highest highest ≥300 mppcf x yr
Armstrong (1988)	Australia/ mining	6,505	1.60	~5	Crocodolite; highest estimated by yrs worked
Gardner (1986)	England/ cement	1,510	0.92	2.24	Highest ≥5f/mL
Hughes (1987)	New Orleans/ cement	6,931	1.13	2.31	Highest ≥1100 mppcf x yr
Albin (1990)	Sweden/ cement	7,465	1.8	1.9	Highest ≥40 f/mL x yr

† Highest exposed defined in various ways (see Comments)

Table V.3
Lung Cancer Relative Risks from Some Published Studies of Man-Made Mineral Fiber Manufacturing Workers

Author (year)	Location	No. workers in cohort	Relative risk: Overall	Relative risk: Highest exposed†	Comments
Robinson (1982)	U.S.	596	0.89	1.33	Highest ≥20 yr employed
Simonato (1987)	7 countries, Europe	21,967	1.25	2.95	Highest ≥30 yr in rock/wool during early phases
Marsh (1990)	U.S.	16,661	1.13	1.18	Highest ≥30 yr mineral wool

† Highest exposed defined in various ways (see Comments)

CHAPTER VI

RECOMMENDATIONS

Our recommendations focus mainly on approaches to exposure monitoring and record keeping that will be necessary for evaluating the health effects of occupational exposures. However, we also feel compelled to make some recommendations about the continuing need for exposure reduction and medical monitoring. At this point, there is not enough information to determine whether conditions that appeared to be hazardous to workers' health still exist at the plants studied. Although the excesses of lung cancer and non-malignant respiratory disease observed in our study were probably related to exposures that occurred during past decades, it is premature to conclude that dust exposure reductions have necessarily created a hazard-free workplace environment.

Continued efforts should be made to reduce exposures where possible through engineering controls, good house-keeping practices, and the use of automated processes. Although respirators are not an acceptable substitution for other feasible controls, they remain an essential component of reducing exposures. Strict enforcement of respirator use is necessary, not only at official work stations, but also in any areas where exposure hazards exist, such as in the vicinity of dusty work stations, spills, and other accidental releases of dust, and in areas where maintenance is performed. A routine medical monitoring program for exposed workers, including chest x-rays, also remains necessary. We recognize that the industry has been following most of these practices in recent years, and strongly support continued vigilance in these efforts.

A. Exposure Monitoring

Exposure monitoring has three main functions. The first, and most obvious, is to identify excessive exposures that pose health risks to workers. Related to that function is the need to ensure that the workplace environment is in compliance with Federal and local standards. The third, and least obvious, purpose of exposure monitoring is to generate a systematic record of exposures received throughout the workplace that can ultimately be linked with employment and health data in an epidemiologic assessment of potential risks.

In this study, we were confronted with the problems of incomplete dust monitoring data for various time periods, and different sample collection techniques for available data that precluded a straightforward conversion of particle counts (mppcf) to the modern gravimetric units (mg/M^3). While it is inevitable that measurement techniques will change over time, it would be useful to determine conversion factors at the the times when changes take place. This could be accomplished by performing side-by-side sampling studies using the old and new dust measurement methods. Such studies need not be extensive plant-wide surveys, but should be conducted in enough locations to permit separate conversions for the major forms of dust. Montgomery's [1991] work in this area is a good example of this strategy.

One major difficulty that is frequently encountered in epidemiologic studies that attempt to use industrial hygiene data, especially data from past years, is that sampling often is performed for compliance purposes, and thus the data may represent "worst case" situations. The net effects of compliance sampling strategies are that exposures for workers in monitored areas are likely to be overestimates of average values, and low or background exposures in some areas cannot be confirmed because measurements are restricted to the presumed heavy exposure jobs and areas. Another problem that often arises with industrial hygiene data is that variability of exposures over time and between workers within the same job category, or performing the same tasks, is unknown because replicate samples were not taken. Thus, it is necessary to devise sampling strategies that permit systematic evaluations of plant-wide levels, including lightly and non-exposed areas, and that take into account intra-area and intra-job variability [Rappaport, 1991; Heedrik et al., 1991]. Of course, cost and feasibility constraints will dictate the extent to which these objectives can be met in an exposure monitoring program. Some practical recommendations for dust monitoring are offered below.

Area dust samples are useful for evaluating house-keeping practices and other dust control measures; however, it is usually difficult to extrapolate area sampling results to workers' actual exposures. Personal samples are much more efficient in this regard. We should point out that the data obtained from personal sampling ultimately are used to construct average exposure profiles for groups of workers sharing common environments and job duties, and not necessarily to associate a particular worker's sampling results with his or her individual exposure profile. Thus, it is more productive and feasible to monitor over time a sample of workers in the various job categories and to derive average job-specific exposure values, than to attempt to obtain exposure data specific for each worker. In order for the results of personal dust samples to be interpretable in the future, a great deal of information should be recorded, including the operation, location, and job title of the sampled employee, the presence of other hazards (e.g., welding fumes), and the use of personal protective equipment.

Industrial hygiene samples are necessary for assessing exposure; however, a comprehensive industrial hygiene program also requires periodic evaluations of workplace conditions by qualified health and safety professionals. Haas [1982] provides a useful checklist for evaluating corporate industrial hygiene programs.

Some ancillary sources of information that are valuable for characterizing dust exposures include: changes in the use of respiratory protection practices and dust ventilation, production records, spill or leak reports, and quality control laboratory data, especially information on crystalline silica and contaminant (e.g., trace metals) contents of the dust. These data should be readily retrievable by the industrial hygiene and safety personnel responsible for exposure monitoring.

B. <u>Record Keeping</u>

The success of industrial hygiene medical and epidemiologic surveillance systems is dependent on thorough and accurate recording of personnel, work history, exposure, and health data. At a minimum, there needs to be a record maintained for each worker hired in the plant that contains the following data items:

1. Full name
2. Gender
3. Race and ethnicity (sometimes determined by birthplace)
4. Date of birth
5. Date of hire
6. Date of termination

The goals of an epidemiologic study are to examine health risks in relation to workplace exposures. Consequently, this minimal list of necessary data items should be augmented with data that permit a determination of length of service in the industry, length of service in specific jobs, and exposures to specific workplace agents (i.e., natural, calcined, and flux-calcined dust). Most important in this regard is the transcription of changes in job titles, work stations, and job tasks, and the dates when such changes occurred. Time spent on lay-offs, military service, or sick leave should also be recorded in the personnel records.

Linkage of work history and exposure data is greatly facilitated when the job titles identified in the exposure monitoring program correspond to those that appear in personnel records. In many industries, job titles change over time, largely due to changes in production, and for other administrative reasons. In fact, there is an increasing trend in some industries to use generic job titles (e.g., "production operator") in place of more descriptive titles. To the extent possible, this trend should be avoided in the DE industry. However, if job titles do change, then a dictionary of job titles and dates of job title changes should be maintained.

It is also desirable to collect information on previous employment, especially in other dusty industries, and smoking habits. This information can be obtained at initial hire, and the smoking information can be updated at periodic x-ray and medical examinations. The minimum detail of smoking information collected is current status (never smoked, current smoker, ex-smoker). Additional data that are valuable for health risk assessment and epidemiologic purposes include: dates started and stopped smoking, amount smoked (e.g., cigarettes per day), and type of cigarettes smoked (filter vs. non-filter). Similar information on pipe and cigar smoking can also be obtained at the same time as cigarette smoking data.

C. Medical Surveillance

Medical surveillance programs are ongoing in each company. These generally consist of periodic x-rays, and in some instances spirometry and other procedures. We are strongly supportive of these programs, and would further suggest following the ILO [1988] guidelines for maintaining updated lists of workers' demographic and medical information to permit linkage with work history and exposure data.

Our final recommendation concerns health promotion among the currently employed workforce. In view of the concern about lung cancer and non-malignant respiratory diseases in the DE industry, it would be sound public health practice to make available to workers educational programs that explain the hazards of occupational dust and smoking.

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APPENDIX

Listing of job titles, exposure level ratings, and product type

Table A.1
Exposure Level and Product Type by Job: Manville, Lompoc Plant

Job Title	Exposure Level	Product Type
10# Station Operator/Packer	High	Flux Calcined
Packer	High	Mixed Calcined
Pack/Refeeder Utility	High	Mixed Calcined
Baghouseman	High	Mixed Calcined
Refeeder	High	Mixed Calcined
Central Waste Load Lugger	High	Mixed Calcined
Dust Leak Patcher	High	Mixed Calcined
Mill/Warehouse Janitor	High	Mixed Calcined
Laborer	High	Mixed Calcined
Bag Reclaimer	High	Mixed Calcined
Other Sack Room Work	High	Mixed Calcined
Sack Cleaner	High	Mixed Calcined
Sewing Machine Operator	High	Mixed Calcined
Lift Truck Operator	High	Mixed Calcined
Carloader	High	Mixed Calcined
Lead - Working	High	Mixed Calcined
Warehouseman	High	Mixed Calcined
Carton Packer	High	Mixed Calcined
Silicate Plant Refeeder	High	Mixed Calcined
Silicate Packer/Trucker	High	Silicate
Packer - Natural	High	Natural
Baghouseman Natural	High	Natural
Brick Cutter	High	Natural
Mortar Plant Oper/Packer*	High	Mixed Calcined
Mixer/Special Product*	High	Mixed Calcined
Sorbo-Cel Helper	Intermediate	Flux Calcined
Sorbo-Cel Mixer	Intermediate	Flux Calcined
Sorbo-Cel Oper	Intermediate	Flux Calcined
Automatic Pack Station Oper	Intermediate	Mixed Calcined
Automatic Refeeder Oper	Intermediate	Mixed Calcined
Bulk Carton Filler	Intermediate	Mixed Calcined
Bulk Operator	Intermediate	Mixed Calcined
Bulk Station Packer	Intermediate	Mixed Calcined
Janitor Mill & Office	Intermediate	Mixed Calcined
Lift Truck Operator	Intermediate	Mixed Calcined
Other Mill Job	Intermediate	Mixed Calcined
Checker	Intermediate	Mixed Calcined
Diesel Transfer Truck	Intermediate	Mixed Calcined
Foreman	Intermediate	Mixed Calcined
Lift Truck Leader	Intermediate	Mixed Calcined
Tite-Pac Operator	Intermediate	Mixed Calcined
Drierman	Intermediate	Mixed Calcined
Hoist Operator	Intermediate	Mixed Calcined

*Jobs with Potential Asbestos Exposure

Exposure Level and Product Type by Job: Manville, Lompoc Plant (cont)

Job Title	Exposure Level	Product Type
Inspector	Intermediate	Mixed Calcined
Lift Truck Operator	Intermediate	Mixed Calcined
Brick Plant Machine Tender	Intermediate	Mixed Calcined
Pugger	Intermediate	Mixed Calcined
Kiln Unload/Packer	Intermediate	Mixed Calcined
Brick Handlers	Intermediate	Mixed Calcined
Brick Plant Controlman	Intermediate	Mixed Calcined
Brick Plant Mechanic	Intermediate	Mixed Calcined
Dollyman Packer C3	Intermediate	Mixed Calcined
Other Brick Plant Jobs	Intermediate	Mixed Calcined
Chromosorb Operator	Intermediate	Mixed Calcined
Pellet Plant Operator	Intermediate	Mixed Calcined
Other Celite Specialties	Intermediate	Mixed Calcined
Other Quality Control	Intermediate	Mixed Calcined
Foreman/Lead	Intermediate	Mixed Calcined
Safety Equip Maint	Intermediate	Mixed Calcined
Maint Supervisors	Intermediate	Mixed Calcined
Bricklayer	Intermediate	Mixed Calcined
Carpenters	Intermediate	Mixed Calcined
Painters	Intermediate	Mixed Calcined
Electricians	Intermediate	Mixed Calcined
Erectors	Intermediate	Mixed Calcined
Garage Workers	Intermediate	Mixed Calcined
Machine Shop	Intermediate	Mixed Calcined
Maintenance	Intermediate	Mixed Calcined
Plumbers	Intermediate	Mixed Calcined
Sheetmetal	Intermediate	Mixed Calcined
Blacksmiths	Intermediate	Mixed Calcined
Welders	Intermediate	Mixed Calcined
Drag & Ruggles Operator	Intermediate	Mixed Calcined
AWFA Operator Packer	Intermediate	Mixed Calcined
Feed Mix Operator	Intermediate	Mixed Calcined
Silicate Plant Maintenance	Intermediate	Silicate
Silicate Plant Janitor	Intermediate	Silicate
Sil. Plant Process Tester	Intermediate	Silicate
Other Silicate Plant Jobs	Intermediate	Silicate
#1 Mill Workers	Intermediate	Natural
Fireman #9 Calciner	Intermediate	Natural
Feeder #9 Calciner	Intermediate	Natural
Natural Brick Inspector	Intermediate	Natural
Natural Brick Packer	Intermediate	Natural
Other Natural Brick Jobs	Intermediate	Natural
Brick Picker	Intermediate	Natural
Sizing Plant Operator	Intermediate	Natural
Brick Pressman	Intermediate	Natural
Special Blockman	Intermediate	Natural

Exposure Level and Product Type by Job: Manville, Lompoc Plant (cont)

Job Title	Exposure Level	Product Type
Kiln Brick Setters	Intermediate	Natural
Crude Tester	Intermediate	Natural
Grader Operator	Intermediate	Natural
Road Scraper Operator	Intermediate	Natural
Water Wagon Operator	Intermediate	Natural
Shovel/Crane Operator	Intermediate	Natural
Bulldozer Operator	Intermediate	Natural
Sampler/Diamond Driller	Intermediate	Natural
Equipment Insp/Trainer	Intermediate	Natural
Leader	Intermediate	Natural
Powderman	Intermediate	Natural
Quarryman	Intermediate	Natural
Quarry Truck Driver	Intermediate	Natural
Shovel Operator	Intermediate	Natural
Quarry/Mines Repair	Intermediate	Natural
Prime Loader	Intermediate	Natural
Other Quarry/Mines Jobs	Intermediate	Natural
Crusherman	Intermediate	Natural
Tunnel A Working Lead	Intermediate	Natural
Locomotive Operator	Intermediate	Natural
Underground Laborer	Intermediate	Natural
Experimental Plant*	Intermediate	Mixed Calcined
Foreman/Supervisors	Light	Mixed Calcined
Controlman	Light	Mixed Calcined
Super Rec & Shipping	Light	Mixed Calcined
Rodman & Other Engineering	Light	Mixed Calcined
Inspector	Light	Mixed Calcined
Lab Assistant	Light	Mixed Calcined
Sampleman	Light	Mixed Calcined
Lab Technician	Light	Mixed Calcined
Store Room	Light	Mixed Calcined
Super Silicates	Light	Silicate
Drier Operator	Light	Silicate
Silicate Plant Operator	Light	Silicate
Boiler Plant Operator	Light	Silicate
Quarry/Mines Supervisor	Light	Natural
Tunnel Supervisor	Light	Natural
Controlman #11 Mill	Light	Natural
Jet/Talc Mill Operator*	Light	Mixed Calcined
Office Workers	None	No DE Exposure
Other Unexposed	None	No DE Exposure

* Jobs with Potential Asbestos Exposure

Table A.2
Exposure Level and Product Type by Job: Grefco, Lompoc Plant

Job Title	Exposure Level	Product Type
Warehouseman	High	Mixed Calcined
Millman	High	Mixed Calcined
Specialty Products*	High	Mixed Calcined
Controlman	Intermediate	Mixed Calcined
Mobile Equipment Operator	Intermediate	Mixed Calcined
General Laborer	Intermediate	Mixed Calcined
Utility Worker	Intermediate	Mixed Calcined
Other Mill Jobs	Intermediate	Mixed Calcined
Maintenance Helper	Intermediate	Mixed Calcined
Maintenance Laborer	Intermediate	Mixed Calcined
Quarry Dozer/Grader	Intermediate	Natural
Quarry Foreman	Intermediate	Natural
Quarry Slusher Operator	Intermediate	Natural
Quarry Rockman	Intermediate	Natural
Misc Quarry Job	Intermediate	Natural
Heavy Equipment Operator	Intermediate	Natural
Lab/QC Supervisors	Light	Mixed Calcined
Lab Technician	Light	Mixed Calcined
Plant Chemists	Light	Mixed Calcined
General Foreman	Light	Mixed Calcined
Yard Foreman/Leaderman	Light	Mixed Calcined
Warehouse Foreman/Leadman	Light	Mixed Calcined
Maintenance Foreman	Light	Mixed Calcined
Bulk Truck Driver	Light	Mixed Calcined
Semi-Tractor Operator	Light	Mixed Calcined
General Mechanic	Light	Mixed Calcined
Craftsman Maintainer	Light	Mixed Calcined
Electrician	Light	Mixed Calcined
Oiler	Light	Mixed Calcined
Painter	Light	Mixed Calcined
Welder	Light	Mixed Calcined
Auto Mechanic	Light	Mixed Calcined
Mining Engineer	Light	Natural
Quarry Supervisor	None	No DE Exposure
Office Jobs	None	No DE Exposure

* Jobs with Potential Asbestos Exposure